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(54) Title: HUMAN KINASES

(57) Abstract: The invention provides human kinases (PKIN) and polynucleotides which identify and encode PKIN. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with aberrant expression of PKIN.

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HUMAN KINASES

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of human kinases and to the
5 use of these sequences in the diagnosis, treatment, and prevention of cancer, immune disorders,
disorders affecting growth and development, cardiovascular diseases, and lipid disorders, and in the
assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid
sequences of human kinases.

10 BACKGROUND OF THE INVENTION

Kinases comprise the largest known enzyme superfamily and vary widely in their target
molecules. Kinases catalyze the transfer of high energy phosphate groups from a phosphate donor to
a phosphate acceptor. Nucleotides usually serve as the phosphate donor in these reactions, with most
kinases utilizing adenosine triphosphate (ATP). The phosphate acceptor can be any of a variety of
15 molecules, including nucleosides, nucleotides, lipids, carbohydrates, and proteins. Proteins are
phosphorylated on hydroxyamino acids. Addition of a phosphate group alters the local charge on the
acceptor molecule, causing internal conformational changes and potentially influencing intermolecular
contacts. Reversible protein phosphorylation is the primary method for regulating protein activity in
eukaryotic cells. In general, proteins are activated by phosphorylation in response to extracellular
20 signals such as hormones, neurotransmitters, and growth and differentiation factors. The activated
proteins initiate the cell's intracellular response by way of intracellular signaling pathways and second
messenger molecules such as cyclic nucleotides, calcium-calmodulin, inositol, and various mitogens,
that regulate protein phosphorylation.

Kinases are involved in all aspects of a cell's function, from basic metabolic processes, such
25 as glycolysis, to cell-cycle regulation, differentiation, and communication with the extracellular
environment through signal transduction cascades. Inappropriate phosphorylation of proteins in cells
has been linked to changes in cell cycle progression and cell differentiation. Changes in the cell cycle
have been linked to induction of apoptosis or cancer. Changes in cell differentiation have been linked
to diseases and disorders of the reproductive system, immune system, and skeletal muscle.

30 There are two classes of protein kinases. One class, protein tyrosine kinases (PTKs),
phosphorylates tyrosine residues, and the other class, protein serine/threonine kinases (STKs),
phosphorylates serine and threonine residues. Some PTKs and STKs possess structural
characteristics of both families and have dual specificity for both tyrosine and serine/threonine
residues. Almost all kinases contain a conserved 250-300 amino acid catalytic domain containing

specific residues and sequence motifs characteristic of the kinase family. The protein kinase catalytic domain can be further divided into 11 subdomains. N-terminal subdomains I-IV fold into a two-lobed structure which binds and orients the ATP donor molecule, and subdomain V spans the two lobes. C-terminal subdomains VI-XI bind the protein substrate and transfer the gamma phosphate from ATP to the hydroxyl group of a tyrosine, serine, or threonine residue. Each of the 11 subdomains contains specific catalytic residues or amino acid motifs characteristic of that subdomain. For example, subdomain I contains an 8-amino acid glycine-rich ATP binding consensus motif, subdomain II contains a critical lysine residue required for maximal catalytic activity, and subdomains VI through IX comprise the highly conserved catalytic core. PTKs and STKs also contain distinct sequence motifs in subdomains VI and VIII which may confer hydroxyamino acid specificity.

In addition, kinases may also be classified by additional amino acid sequences, generally between 5 and 100 residues, which either flank or occur within the kinase domain. These additional amino acid sequences regulate kinase activity and determine substrate specificity. (Reviewed in Hardie, G. and S. Hanks (1995) The Protein Kinase Facts Book, Vol I, pp. 17-20 Academic Press, San Diego CA.). In particular, two protein kinase signature sequences have been identified in the kinase domain, the first containing an active site lysine residue involved in ATP binding, and the second containing an aspartate residue important for catalytic activity. If a protein analyzed includes the two protein kinase signatures, the probability of that protein being a protein kinase is close to 100% (PROSITE: PDOC00100, November 1995).

Protein Tyrosine Kinases

Protein tyrosine kinases (PTKs) may be classified as either transmembrane, receptor PTKs or nontransmembrane, nonreceptor PTK proteins. Transmembrane tyrosine kinases function as receptors for most growth factors. Growth factors bind to the receptor tyrosine kinase (RTK), which causes the receptor to phosphorylate itself (autophosphorylation) and specific intracellular second messenger proteins. Growth factors (GF) that associate with receptor PTKs include epidermal GF, platelet-derived GF, fibroblast GF, hepatocyte GF, insulin and insulin-like GFs, nerve GF, vascular endothelial GF, and macrophage colony stimulating factor.

Nontransmembrane, nonreceptor PTKs lack transmembrane regions and, instead, form signaling complexes with the cytosolic domains of plasma membrane receptors. Receptors that function through non-receptor PTKs include those for cytokines and hormones (growth hormone and prolactin), and antigen-specific receptors on T and B lymphocytes.

Many PTKs were first identified as oncogene products in cancer cells in which PTK activation was no longer subject to normal cellular controls. In fact, about one third of the known oncogenes encode PTKs. Furthermore, cellular transformation (oncogenesis) is often accompanied

by increased tyrosine phosphorylation activity (Charbonneau, H. and N.K. Tonks (1992) *Annu. Rev. Cell Biol.* 8:463-493). Regulation of PTK activity may therefore be an important strategy in controlling some types of cancer.

Substrates for tyrosine kinases can be identified using anti-phosphotyrosine antibodies to screen tyrosine-phosphorylated cDNA expression libraries. Fish, so named for tyrosine-phosphorylated in Src-transformed fibroblast, is a tyrosine kinase substrate which has been identified by such a technique. Fish has five SH3 domains and a phospho homology (PX) domain. Fish is suggested to be involved in signalling by tyrosine kinases and have a role in the actin cytoskeleton (Lock, P. et al (1998) *EMBO J.* 17:4346-4357).

SHP-2, an SH2-domain-containing phosphotyrosine phosphatase, is a positive signal transducer for several receptor tyrosine kinases (RTKs) and cytokine receptors. Phosphotyrosine phosphatases are critical positive and negative regulators in the intracellular signalling pathways that result in growth-factor-specific cell responses such as mitosis, migration, differentiation, transformation, survival or death. Signal-regulatory proteins (SIRPs) comprise a new gene family of at least 15 members, consisting of two subtypes distinguished by the presence or absence of a cytoplasmic SHP-2-binding domain. The SIRP-alpha subfamily members have a cytoplasmic SHP2-binding domain and includes SIRP-alpha-1, a transmembrane protein, a substrate of activated RTKs and which binds to SH2 domains. SIRPs have a high degree of homology with immune antigen recognition molecules. The SIRP-beta subfamily lacks the cytoplasmic tail. The SIRP-beta-1 gene encodes a polypeptide of 398 amino acids. SIRP family members are generally involved in regulation of signals which define different physiological and pathological processes (Kharitonov, A. et al (1997) *Nature* 386:181-186). Two possible areas of regulation include determination of brain diversity and genetic individuality (Sano, S et al (1999) *Biochem. J.* 344 Pt 3:667-675) and recognition of self which fails in diseases such as hemolytic anemia (Oldenburg, P.-A et al (2000) *Science* 288:2051-2054).

Protein Serine/Threonine Kinases

Protein serine/threonine kinases (STKs) are nontransmembrane proteins. A subclass of STKs are known as ERKs (extracellular signal regulated kinases) or MAPs (mitogen-activated protein kinases) and are activated after cell stimulation by a variety of hormones and growth factors. Cell stimulation induces a signaling cascade leading to phosphorylation of MEK (MAP/ERK kinase) which, in turn, activates ERK via serine and threonine phosphorylation. A varied number of proteins represent the downstream effectors for the active ERK and implicate it in the control of cell proliferation and differentiation, as well as regulation of the cytoskeleton. Activation of ERK is normally transient, and cells possess dual specificity phosphatases that are responsible for its down-regulation. Also, numerous studies have shown that elevated ERK activity is associated with some

cancers. Other STKs include the second messenger dependent protein kinases such as the cyclic-AMP dependent protein kinases (PKA), calcium-calmodulin (CaM) dependent protein kinases, and the mitogen-activated protein kinases (MAP); the cyclin-dependent protein kinases; checkpoint and cell cycle kinases; Numb-associated kinase (Nak); human Fused (hFu); proliferation-related
 5 kinases; 5'-AMP-activated protein kinases; and kinases involved in apoptosis.

The second messenger dependent protein kinases primarily mediate the effects of second messengers such as cyclic AMP (cAMP), cyclic GMP, inositol triphosphate, phosphatidylinositol, 3,4,5-triphosphate, cyclic ADP ribose, arachidonic acid, diacylglycerol and calcium-calmodulin. The PKAs are involved in mediating hormone-induced cellular responses and are activated by cAMP
 10 produced within the cell in response to hormone stimulation. cAMP is an intracellular mediator of hormone action in all animal cells that have been studied. Hormone-induced cellular responses include thyroid hormone secretion, cortisol secretion, progesterone secretion, glycogen breakdown, bone resorption, and regulation of heart rate and force of heart muscle contraction. PKA is found in all animal cells and is thought to account for the effects of cAMP in most of these cells. Altered PKA
 15 expression is implicated in a variety of disorders and diseases including cancer, thyroid disorders, diabetes, atherosclerosis, and cardiovascular disease (Isselbacher, K.J. et al. (1994) Harrison's Principles of Internal Medicine, McGraw-Hill, New York NY, pp. 416-431, 1887).

The casein kinase I (CKI) gene family is another subfamily of serine/threonine protein kinases. This continuously expanding group of kinases have been implicated in the regulation of
 20 numerous cytoplasmic and nuclear processes, including cell metabolism, and DNA replication and repair. CKI enzymes are present in the membranes, nucleus, cytoplasm and cytoskeleton of eukaryotic cells, and on the mitotic spindles of mammalian cells (Fish, K.J. et al. (1995) J. Biol. Chem. 270:14875-14883).

The CKI family members all have a short amino-terminal domain of 9-76 amino acids, a highly
 25 conserved kinase domain of 284 amino acids, and a variable carboxyl-terminal domain that ranges from 24 to over 200 amino acids in length (Cegielska, A. et al. (1998) J. Biol. Chem. 273:1357-1364). The CKI family is comprised of highly related proteins, as seen by the identification of isoforms of casein kinase I from a variety of sources. There are at least five mammalian isoforms, α , β , γ , δ , and ϵ . Fish et al., identified CKI-epsilon from a human placenta cDNA library. It is a basic protein of 416
 30 amino acids and is closest to CKI-delta. Through recombinant expression, it was determined to phosphorylate known CKI substrates and was inhibited by the CKI-specific inhibitor CKI-7. The human gene for CKI-epsilon was able to rescue yeast with a slow-growth phenotype caused by deletion of the yeast CKI locus, HRR250 (Fish et al., supra).

The mammalian circadian mutation tau was found to be a semidominant autosomal allele of

CKI-epsilon that markedly shortens period length of circadian rhythms in Syrian hamsters. The tau locus is encoded by casein kinase I-epsilon, which is also a homolog of the *Drosophila* circadian gene double-time. Studies of both the wildtype and tau mutant CKI-epsilon enzyme indicated that the mutant enzyme has a noticeable reduction in the maximum velocity and autophosphorylation state.

5 Further, *in vitro*, CKI-epsilon is able to interact with mammalian PERIOD proteins, while the mutant enzyme is deficient in its ability to phosphorylate PERIOD. Lowrey et al., have proposed that CKI-epsilon plays a major role in delaying the negative feedback signal within the transcription-translation-based autoregulatory loop that composes the core of the circadian mechanism. Therefore the CKI-epsilon enzyme is an ideal target for pharmaceutical compounds influencing circadian rhythms, jet-lag

10 and sleep, in addition to other physiologic and metabolic processes under circadian regulation (Lowrey, P.L. et al. (2000) Science 288:483-491).

Homeodomain-interacting protein kinases (HIPKs) are serine/threonine kinases and novel members of the DYRK kinase subfamily (Hofmann, T.G. et al. (2000) Biochimie 82:1123-1127). HIPKs contain a conserved protein kinase domain separated from a domain that interacts with

15 homeoproteins. HIPKs are nuclear kinases, and HIPK2 is highly expressed in neuronal tissue (Kim, Y.H. et al. (1998) J. Biol. Chem. 273:25875-25879; Wang, Y. et al. (2001) Biochim. Biophys. Acta 1518:168-172). HIPKs act as corepressors for homeodomain transcription factors. This corepressor activity is seen in posttranslational modifications such as ubiquitination and phosphorylation, each of which are important in the regulation of cellular protein function (Kim, Y.H. et al. (1999) Proc. Natl.

20 Acad. Sci. USA 96:12350-12355).

The UNC-51 serine/threonine kinase of *Caenorhabditis elegans* is required for axon formation. Its murine homolog is expressed in granule cells of the cerebellar cortex (Tomoda, T. et al. (1999) Neuron 24:833-846). The human homolog of UNC-51, ULK1 (UNC-51 (*C. elegans*)-like kinase 1), is highly conserved among vertebrates. It is composed of 1050 amino acids, has a

25 calculated MW of 112.6 kDa and a pI of 8.80. ULK1 is ubiquitously expressed in adult tissues while UNC-51 has been specifically located in the nervous system of *C. elegans*. ULK1 has been mapped to human chromosome 12q24.3 (Kuroyanagi, H. et al. (1998) Genomics 51:76-85).

Calcium-Calmodulin Dependent Protein Kinases

Calcium-calmodulin dependent (CaM) kinases are involved in regulation of smooth muscle

30 contraction, glycogen breakdown (phosphorylase kinase), and neurotransmission (CaM kinase I and CaM kinase II). CaM dependent protein kinases are activated by calmodulin, an intracellular calcium receptor, in response to the concentration of free calcium in the cell. Many CaM kinases are also activated by phosphorylation. Some CaM kinases are also activated by autophosphorylation or by other regulatory kinases. CaM kinase I phosphorylates a variety of substrates including the

neurotransmitter-related proteins synapsin I and II, the gene transcription regulator, CREB, and the cystic fibrosis conductance regulator protein, CFTR (Haribabu, B. et al. (1995) EMBO J. 14:3679-3686). CaM kinase II also phosphorylates synapsin at different sites and controls the synthesis of catecholamines in the brain through phosphorylation and activation of tyrosine hydroxylase. CaM kinase II controls the synthesis of catecholamines and serotonin, through phosphorylation/activation of tyrosine hydroxylase and tryptophan hydroxylase, respectively (Fujisawa, H. (1990) BioEssays 12:27-29). The mRNA encoding a calmodulin-binding protein kinase-like protein was found to be enriched in mammalian forebrain. This protein is associated with vesicles in both axons and dendrites and accumulates largely postnatally. The amino acid sequence of this protein is similar to CaM-dependent STKs, and the protein binds calmodulin in the presence of calcium (Godbout, M. et al. (1994) J. Neurosci. 14:1-13).

Mitogen-Activated Protein Kinases

The mitogen-activated protein kinases (MAP) which mediate signal transduction from the cell surface to the nucleus via phosphorylation cascades are another STK family that regulates intracellular signaling pathways. Several subgroups have been identified, and each manifests different substrate specificities and responds to distinct extracellular stimuli (Egan, S.E. and R.A. Weinberg (1993) Nature 365:781-2483). There are 3-kinase modules comprising the MAP kinase cascade: MAPK (MAP), MAPK kinase (MAP2K, MAPKK, or MKK), and MKK kinase (MAP3K, MAPKKK, OR MEKK) (Wang, X.S. et al (1998) Biochem. Biophys. Res. Commun. 253:33-37). The extracellular-regulated kinase (ERK) pathway is activated by growth factors and mitogens, for example, epidermal growth factor (EGF), ultraviolet light, hyperosmolar medium, heat shock, endotoxic lipopolysaccharide (LPS). The closely related though distinct parallel pathways, the c-Jun N-terminal kinase (JNK), or stress-activated kinase (SAPK) pathway, and the p38 kinase pathway are activated by stress stimuli and proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1). Altered MAP kinase expression is implicated in a variety of disease conditions including cancer, inflammation, immune disorders, and disorders affecting growth and development.. MAP kinase signaling pathways are present in mammalian cells as well as in yeast.

MAPKKK6 (MAP3K6) is one of numerous MAP3Ks identified. Isolated from skeletal muscle, MAP3K6 is 1,280 amino acids in length with 11 kinase subdomains and is detected in several tissues. The highest expression has been found in heart and skeletal muscle. MAP3K6 has 45% amino acid sequence identity with MAP3K5, while their catalytic domains share 82% identity. MAP3K6 interaction with MAP3K5 *in vivo* was confirmed by coimmunoprecipitation. Recombinant MAP3K6 has been shown to weakly activate the JNK but not the p38 kinase or ERK pathways (Wang, X.S. et al. *supra*)

Cyclin-Dependent Protein Kinases

The cyclin-dependent protein kinases (CDKs) are STKs that control the progression of cells through the cell cycle. The entry and exit of a cell from mitosis are regulated by the synthesis and destruction of a family of activating proteins called cyclins. Cyclins are small regulatory proteins that bind to and activate CDKs, which then phosphorylate and activate selected proteins involved in the mitotic process. CDKs are unique in that they require multiple inputs to become activated. In addition to cyclin binding, CDK activation requires the phosphorylation of a specific threonine residue and the dephosphorylation of a specific tyrosine residue on the CDK.

Another family of STKs associated with the cell cycle are the NIMA (never in mitosis)-related kinases (Neks). Both CDKs and Neks are involved in duplication, maturation, and separation of the microtubule organizing center, the centrosome, in animal cells (Fry, A.M. et al. (1998) EMBO J. 17:470-481).

Checkpoint and Cell Cycle Kinases

In the process of cell division, the order and timing of cell cycle transitions are under control of cell cycle checkpoints, which ensure that critical events such as DNA replication and chromosome segregation are carried out with precision. If DNA is damaged, e.g. by radiation, a checkpoint pathway is activated that arrests the cell cycle to provide time for repair. If the damage is extensive, apoptosis is induced. In the absence of such checkpoints, the damaged DNA is inherited by aberrant cells which may cause proliferative disorders such as cancer. Protein kinases play an important role in this process. For example, a specific kinase, checkpoint kinase 1 (Chk1), has been identified in yeast and mammals, and is activated by DNA damage in yeast. Activation of Chk1 leads to the arrest of the cell at the G2/M transition (Sanchez, Y. et al. (1997) Science 277:1497-1501). Specifically, Chk1 phosphorylates the cell division cycle phosphatase CDC25, inhibiting its normal function which is to dephosphorylate and activate the cyclin-dependent kinase Cdc2. Cdc2 activation controls the entry of cells into mitosis (Peng, C.-Y. et al. (1997) Science 277:1501-1505). Thus, activation of Chk1 prevents the damaged cell from entering mitosis. A similar deficiency in a checkpoint kinase, such as Chk1, may also contribute to cancer by failure to arrest cells with damaged DNA at other checkpoints such as G2/M.

Proliferation-Related Kinases

Proliferation-related kinase is a serum/cytokine inducible STK that is involved in regulation of the cell cycle and cell proliferation in human megakaryocytic cells (Li, B. et al. (1996) J. Biol. Chem. 271:19402-19408). Proliferation-related kinase is related to the polo (derived from *Drosophila* polo gene) family of STKs implicated in cell division. Proliferation-related kinase is downregulated in lung tumor tissue and may be a proto-oncogene whose deregulated expression in normal tissue leads to

oncogenic transformation.

5'-AMP-activated protein kinase

A ligand-activated STK protein kinase is 5'-AMP-activated protein kinase (AMPK) (Gao, G. et al. (1996) J. Biol Chem. 271:8675-8681). Mammalian AMPK is a regulator of fatty acid and sterol synthesis through phosphorylation of the enzymes acetyl-CoA carboxylase and hydroxymethylglutaryl-CoA reductase and mediates responses of these pathways to cellular stresses such as heat shock and depletion of glucose and ATP. AMPK is a heterotrimeric complex comprised of a catalytic alpha subunit and two non-catalytic beta and gamma subunits that are believed to regulate the activity of the alpha subunit. Subunits of AMPK have a much wider distribution in non-lipogenic tissues such as brain, heart, spleen, and lung than expected. This distribution suggests that its role may extend beyond regulation of lipid metabolism alone.

Kinases in Apoptosis

Apoptosis is a highly regulated signaling pathway leading to cell death that plays a crucial role in tissue development and homeostasis. Deregulation of this process is associated with the pathogenesis of a number of diseases including autoimmune disease, neurodegenerative disorders, and cancer. Various STKs play key roles in this process. ZIP kinase is an STK containing a C-terminal leucine zipper domain in addition to its N-terminal protein kinase domain. This C-terminal domain appears to mediate homodimerization and activation of the kinase as well as interactions with transcription factors such as activating transcription factor, ATF4, a member of the cyclic-AMP responsive element binding protein (ATF/CREB) family of transcriptional factors (Sanjo, H. et al. (1998) J. Biol. Chem. 273:29066-29071). DRAK1 and DRAK2 are STKs that share homology with the death-associated protein kinases (DAP kinases), known to function in interferon- γ induced apoptosis (Sanjo et al., *supra*). Like ZIP kinase, DAP kinases contain a C-terminal protein-protein interaction domain, in the form of ankyrin repeats, in addition to the N-terminal kinase domain. ZIP, DAP, and DRAK kinases induce morphological changes associated with apoptosis when transfected into NIH3T3 cells (Sanjo et al., *supra*). However, deletion of either the N-terminal kinase catalytic domain or the C-terminal domain of these proteins abolishes apoptosis activity, indicating that in addition to the kinase activity, activity in the C-terminal domain is also necessary for apoptosis, possibly as an interacting domain with a regulator or a specific substrate.

RICK is another STK recently identified as mediating a specific apoptotic pathway involving the death receptor, CD95 (Inohara, N. et al. (1998) J. Biol. Chem. 273:12296-12300). CD95 is a member of the tumor necrosis factor receptor superfamily and plays a critical role in the regulation and homeostasis of the immune system (Nagata, S. (1997) Cell 88:355-365). The CD95 receptor signaling pathway involves recruitment of various intracellular molecules to a receptor complex

following ligand binding. This process includes recruitment of the cysteine protease caspase-8 which, in turn, activates a caspase cascade leading to cell death. RICK is composed of an N-terminal kinase catalytic domain and a C-terminal "caspase-recruitment" domain that interacts with caspase-like domains, indicating that RICK plays a role in the recruitment of caspase-8. This interpretation is supported by the fact that the expression of RICK in human 293T cells promotes activation of caspase-8 and potentiates the induction of apoptosis by various proteins involved in the CD95 apoptosis pathway (Inohara et al., supra).

Mitochondrial Protein Kinases

A novel class of eukaryotic kinases, related by sequence to prokaryotic histidine protein kinases, are the mitochondrial protein kinases (MPKs) which seem to have no sequence similarity with other eukaryotic protein kinases. These protein kinases are located exclusively in the mitochondrial matrix space and may have evolved from genes originally present in respiration-dependent bacteria which were endocytosed by primitive eukaryotic cells. MPKs are responsible for phosphorylation and inactivation of the branched-chain alpha-ketoacid dehydrogenase and pyruvate dehydrogenase complexes (Harris, R.A. et al. (1995) Adv. Enzyme Regul. 34:147-162). Five MPKs have been identified. Four members correspond to pyruvate dehydrogenase kinase isozymes, regulating the activity of the pyruvate dehydrogenase complex, which is an important regulatory enzyme at the interface between glycolysis and the citric acid cycle. The fifth member corresponds to a branched-chain alpha-ketoacid dehydrogenase kinase, important in the regulation of the pathway for the disposal of branched-chain amino acids. (Harris, R.A. et al. (1997) Adv. Enzyme Regul. 37:271-293). Both starvation and the diabetic state are known to result in a great increase in the activity of the pyruvate dehydrogenase kinase in the liver, heart and muscle of the rat. This increase contributes in both disease states to the phosphorylation and inactivation of the pyruvate dehydrogenase complex and conservation of pyruvate and lactate for gluconeogenesis (Harris (1995) supra).

KINASES WITH NON-PROTEIN SUBSTRATES

Lipid and Inositol kinases

Lipid kinases phosphorylate hydroxyl residues on lipid head groups. A family of kinases involved in phosphorylation of phosphatidylinositol (PI) has been described, each member phosphorylating a specific carbon on the inositol ring (Leevers, S.J. et al. (1999) Curr. Opin. Cell Biol. 11:219-225). The phosphorylation of phosphatidylinositol is involved in activation of the protein kinase C signaling pathway. The inositol phospholipids (phosphoinositides) intracellular signaling pathway begins with binding of a signaling molecule to a G-protein linked receptor in the plasma membrane.

This leads to the phosphorylation of phosphatidylinositol (PI) residues on the inner side of the plasma membrane by inositol kinases, thus converting PI residues to the biphosphate state (PIP_2). PIP_2 is then cleaved into inositol triphosphate (IP_3) and diacylglycerol. These two products act as mediators for separate signaling pathways. Cellular responses that are mediated by these pathways are

5 glycogen breakdown in the liver in response to vasopressin, smooth muscle contraction in response to acetylcholine, and thrombin-induced platelet aggregation.

PI 3-kinase (PI3K), which phosphorylates the D3 position of PI and its derivatives, has a central role in growth factor signal cascades involved in cell growth, differentiation, and metabolism. PI3K is a heterodimer consisting of an adapter subunit and a catalytic subunit. The adapter subunit

10 acts as a scaffolding protein, interacting with specific tyrosine-phosphorylated proteins, lipid moieties, and other cytosolic factors. When the adapter subunit binds tyrosine phosphorylated targets, such as the insulin responsive substrate (IRS)-1, the catalytic subunit is activated and converts PI (4,5) biphosphate (PIP_2) to PI (3,4,5) P_3 (PIP_3). PIP_3 then activates a number of other proteins, including PKA, protein kinase B (PKB), protein kinase C (PKC), glycogen synthase kinase (GSK)-3, and p70

15 ribosomal s6 kinase. PI3K also interacts directly with the cytoskeletal organizing proteins, Rac, rho, and cdc42 (Shepherd, P.R. et al. (1998) Biochem. J. 333:471-490). Animal models for diabetes, such as *obese* and *fat* mice, have altered PI3K adapter subunit levels. Specific mutations in the adapter subunit have also been found in an insulin-resistant Danish population, suggesting a role for PI3K in type-2 diabetes (Shepard, supra).

20 An example of lipid kinase phosphorylation activity is the phosphorylation of D-erythro-sphingosine to the sphingolipid metabolite, sphingosine-1-phosphate (SPP). SPP has emerged as a novel lipid second-messenger with both extracellular and intracellular actions (Kohama, T. et al. (1998) J. Biol. Chem. 273:23722-23728). Extracellularly, SPP is a ligand for the G-protein coupled receptor EDG-1 (endothelial-derived, G-protein coupled receptor). Intracellularly, SPP

25 regulates cell growth, survival, motility, and cytoskeletal changes. SPP levels are regulated by sphingosine kinases that specifically phosphorylate D-erythro-sphingosine to SPP. The importance of sphingosine kinase in cell signaling is indicated by the fact that various stimuli, including platelet-derived growth factor (PDGF), nerve growth factor, and activation of protein kinase C, increase cellular levels of SPP by activation of sphingosine kinase, and the fact that competitive

30 inhibitors of the enzyme selectively inhibit cell proliferation induced by PDGF (Kohama et al., supra).

Purine Nucleotide Kinases

The purine nucleotide kinases, adenylate kinase (ATP:AMP phosphotransferase, or AdK) and guanylate kinase (ATP:GMP phosphotransferase, or GuK) play a key role in nucleotide metabolism and are crucial to the synthesis and regulation of cellular levels of ATP and GTP, respectively. These

two molecules are precursors in DNA and RNA synthesis in growing cells and provide the primary source of biochemical energy in cells (ATP), and signal transduction pathways (GTP). Inhibition of various steps in the synthesis of these two molecules has been the basis of many antiproliferative drugs for cancer and antiviral therapy (Pillwein, K. et al. (1990) Cancer Res. 50:1576-1579).

5 AdK is found in almost all cell types and is especially abundant in cells having high rates of ATP synthesis and utilization such as skeletal muscle. In these cells AdK is physically associated with mitochondria and myofibrils, the subcellular structures that are involved in energy production and utilization, respectively. Recent studies have demonstrated a major function for AdK in transferring high energy phosphoryls from metabolic processes generating ATP to cellular components consuming ATP (Zelevnikar, R.J. et al. (1995) J. Biol. Chem. 270:7311-7319). Thus AdK may have a pivotal
10 role in maintaining energy production in cells, particularly those having a high rate of growth or metabolism such as cancer cells, and may provide a target for suppression of its activity to treat certain cancers. Alternatively, reduced AdK activity may be a source of various metabolic, muscle-energy disorders that can result in cardiac or respiratory failure and may be treatable by
15 increasing AdK activity.

GuK, in addition to providing a key step in the synthesis of GTP for RNA and DNA synthesis, also fulfills an essential function in signal transduction pathways of cells through the regulation of GDP and GTP. Specifically, GTP binding to membrane associated G proteins mediates the activation of cell receptors, subsequent intracellular activation of adenyl cyclase, and production of the second
20 messenger, cyclic AMP. GDP binding to G proteins inhibits these processes. GDP and GTP levels also control the activity of certain oncogenic proteins such as p21^{ras} known to be involved in control of cell proliferation and oncogenesis (Bos, J.L. (1989) Cancer Res. 49:4682-4689). High ratios of GTP:GDP caused by suppression of GuK cause activation of p21^{ras} and promote oncogenesis. Increasing GuK activity to increase levels of GDP and reduce the GTP:GDP ratio may provide a
25 therapeutic strategy to reverse oncogenesis.

GuK is an important enzyme in the phosphorylation and activation of certain antiviral drugs useful in the treatment of herpes virus infections. These drugs include the guanine homologs acyclovir and bucciclovir (Miller, W.H. and R.L. Miller (1980) J. Biol. Chem. 255:7204-7207; Stenberg, K. et al. (1986) J. Biol. Chem. 261:2134-2139). Increasing GuK activity in infected cells may provide a
30 therapeutic strategy for augmenting the effectiveness of these drugs and possibly for reducing the necessary dosages of the drugs.

Pyrimidine Kinases

The pyrimidine kinases are deoxycytidine kinase and thymidine kinase 1 and 2. Deoxycytidine kinase is located in the nucleus, and thymidine kinase 1 and 2 are found in the cytosol (Johansson, M.

et al. (1997) Proc. Natl. Acad. Sci. USA 94:11941-11945). Phosphorylation of deoxyribonucleosides by pyrimidine kinases provides an alternative pathway for de novo synthesis of DNA precursors. The role of pyrimidine kinases, like purine kinases, in phosphorylation is critical to the activation of several chemotherapeutically important nucleoside analogues (Arner E.S. and S. Eriksson (1995) Pharmacol. Ther. 67:155-186).

The discovery of new human kinases, and the polynucleotides encoding them, satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of cancer, immune disorders, disorders affecting growth and development, cardiovascular diseases, and lipid disorders, and in the assessment of the effects of exogenous compounds on the expression of nucleic acid and amino acid sequences of human kinases.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, human kinases, referred to collectively as "PKIN" and individually as "PKIN-1," "PKIN-2," "PKIN-3," "PKIN-4," "PKIN-5," "PKIN-6," "PKIN-7," "PKIN-8," "PKIN-9," "PKIN-10," "PKIN-11," "PKIN-12," "PKIN-13," "PKIN-14," "PKIN-15," "PKIN-16," "PKIN-17," "PKIN-18," "PKIN-19," "PKIN-20," "PKIN-21," "PKIN-22," "PKIN-23," and "PKIN-24." In one aspect, the invention provides an isolated polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-24.

The invention further provides an isolated polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. In one alternative, the polynucleotide encodes a polypeptide selected from the group consisting of SEQ ID NO:1-24. In another alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:25-48.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.

The invention further provides an isolated polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). In one alternative, the polynucleotide

comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). The method comprises a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide selected from the group consisting of a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, c) a polynucleotide complementary to the polynucleotide of a), d) a polynucleotide complementary to the polynucleotide of b), and e) an RNA equivalent of a)-d). The method comprises a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

The invention further provides a composition comprising an effective amount of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and a pharmaceutically acceptable excipient. In one embodiment, the composition comprises an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. The invention additionally provides a method of treating a disease or condition associated with decreased expression of

functional PKIN, comprising administering to a patient in need of such treatment the composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional PKIN, comprising administering to a patient in need of such treatment the composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional PKIN, comprising administering to a patient in need of such treatment the composition.

The invention further provides a method of screening for a compound that specifically binds to a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group

consisting of SEQ ID NO:1-24. The method comprises a) combining the polypeptide with at least one test compound under suitable conditions, and b) detecting binding of the polypeptide to the test compound, thereby identifying a compound that specifically binds to the polypeptide.

The invention further provides a method of screening for a compound that modulates the activity of a polypeptide selected from the group consisting of a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24. The method comprises a) combining the polypeptide with at least one test compound under conditions permissive for the activity of the polypeptide, b) assessing the activity of the polypeptide in the presence of the test compound, and c) comparing the activity of the polypeptide in the presence of the test compound with the activity of the polypeptide in the absence of the test compound, wherein a change in the activity of the polypeptide in the presence of the test compound is indicative of a compound that modulates the activity of the polypeptide.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

The invention further provides a method for assessing toxicity of a test compound, said method comprising a) treating a biological sample containing nucleic acids with the test compound; b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, ii) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, iii) a polynucleotide having a sequence complementary to i), iv) a polynucleotide complementary to the polynucleotide of ii), and v) an RNA equivalent of i)-iv). Hybridization occurs under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide selected from the group consisting of i) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, ii) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a

polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48, iii) a polynucleotide complementary to the polynucleotide of i), iv) a polynucleotide complementary to the polynucleotide of ii), and v) an RNA equivalent of i)-iv). Alternatively, the target polynucleotide comprises a fragment of a polynucleotide sequence selected from the group consisting of i)-v) above; c) quantifying the amount of hybridization complex; and d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is indicative of toxicity of the test compound.

BRIEF DESCRIPTION OF THE TABLES

Table 1 summarizes the nomenclature for the full length polynucleotide and polypeptide sequences of the present invention.

Table 2 shows the GenBank identification number and annotation of the nearest GenBank homolog for polypeptides of the invention. The probability score for the match between each polypeptide and its GenBank homolog is also shown.

Table 3 shows structural features of polypeptide sequences of the invention, including predicted motifs and domains, along with the methods, algorithms, and searchable databases used for analysis of the polypeptides.

Table 4 lists the cDNA and/or genomic DNA fragments which were used to assemble polynucleotide sequences of the invention, along with selected fragments of the polynucleotide sequences.

Table 5 shows the representative cDNA library for polynucleotides of the invention.

Table 6 provides an appendix which describes the tissues and vectors used for construction of the cDNA libraries shown in Table 5.

Table 7 shows the tools, programs, and algorithms used to analyze the polynucleotides and polypeptides of the invention, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an,"

and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to “a host cell” includes a plurality of such host cells, and a reference to “an antibody” is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

5 Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the
10 cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

“PKIN” refers to the amino acid sequences of substantially purified PKIN obtained from any
15 species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term “agonist” refers to a molecule which intensifies or mimics the biological activity of PKIN. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of PKIN either by directly interacting with
20 PKIN or by acting on components of the biological pathway in which PKIN participates.

An “allelic variant” is an alternative form of the gene encoding PKIN. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to
25 allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

“Altered” nucleic acid sequences encoding PKIN include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as PKIN or a
30 polypeptide with at least one functional characteristic of PKIN. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding PKIN, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding PKIN. The encoded protein may also be “altered,” and may contain deletions, insertions, or substitutions of amino

acid residues which produce a silent change and result in a functionally equivalent PKIN. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of PKIN is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of PKIN. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of PKIN either by directly interacting with PKIN or by acting on components of the biological pathway in which PKIN participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, F(ab')₂, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind PKIN polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on

the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition capable of base-pairing with the "sense" (coding) strand of a specific nucleic acid sequence. Antisense compositions may include DNA; RNA; peptide nucleic acid (PNA); oligonucleotides having modified backbone linkages such as phosphorothioates, methylphosphonates, or benzylphosphonates; oligonucleotides having modified sugar groups such as 2'-methoxyethyl sugars or 2'-methoxyethoxy sugars; or oligonucleotides having modified bases such as 5-methyl cytosine, 2'-deoxyuracil, or 7-deaza-2'-deoxyguanosine. Antisense molecules may be produced by any method including chemical synthesis or transcription. Once introduced into a cell, the complementary antisense molecule base-pairs with a naturally occurring nucleic acid sequence produced by the cell to form duplexes which block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand of a reference DNA molecule.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" or "immunogenic" refers to the capability of the natural, recombinant, or synthetic PKIN, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

"Complementary" describes the relationship between two single-stranded nucleic acid sequences that anneal by base-pairing. For example, 5'-AGT-3' pairs with its complement, 3'-TCA-5'.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding PKIN or fragments of PKIN may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been subjected to repeated DNA sequence analysis to resolve uncalled bases, extended using the XL-PCR kit (Applied Biosystems, Foster City CA) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from one or more overlapping cDNA, EST, or genomic DNA fragments using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison

WI) or Phrap (University of Washington, Seattle WA). Some sequences have been both extended and assembled to produce the consensus sequence.

“Conservative amino acid substitutions” are those substitutions that are predicted to least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

| | Original Residue | Conservative Substitution |
|----|------------------|---------------------------|
| | Ala | Gly, Ser |
| 10 | Arg | His, Lys |
| | Asn | Asp, Gln, His |
| | Asp | Asn, Glu |
| | Cys | Ala, Ser |
| | Gln | Asn, Glu, His |
| 15 | Glu | Asp, Gln, His |
| | Gly | Ala |
| | His | Asn, Arg, Gln, Glu |
| | Ile | Leu, Val |
| | Leu | Ile, Val |
| 20 | Lys | Arg, Gln, Glu |
| | Met | Leu, Ile |
| | Phe | His, Met, Leu, Trp, Tyr |
| | Ser | Cys, Thr |
| | Thr | Ser, Val |
| 25 | Trp | Phe, Tyr |
| | Tyr | His, Phe, Trp |
| | Val | Ile, Leu, Thr |

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A “deletion” refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term “derivative” refers to a chemically modified polynucleotide or polypeptide.

Chemical modifications of a polynucleotide can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A “detectable label” refers to a reporter molecule or enzyme that is capable of generating a

measurable signal and is covalently or noncovalently joined to a polynucleotide or polypeptide.

“Differential expression” refers to increased or upregulated; or decreased, downregulated, or absent gene or protein expression, determined by comparing at least two different samples. Such comparisons may be carried out between, for example, a treated and an untreated sample, or a diseased and a normal sample.

“Exon shuffling” refers to the recombination of different coding regions (exons). Since an exon may represent a structural or functional domain of the encoded protein, new proteins may be assembled through the novel reassortment of stable substructures, thus allowing acceleration of the evolution of new protein functions.

A “fragment” is a unique portion of PKIN or the polynucleotide encoding PKIN which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 16, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50%) of a polypeptide as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:25-48 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:25-48, for example, as distinct from any other sequence in the genome from which the fragment was obtained. A fragment of SEQ ID NO:25-48 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:25-48 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:25-48 and the region of SEQ ID NO:25-48 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-24 is encoded by a fragment of SEQ ID NO:25-48. A fragment of SEQ ID NO:1-24 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-24. For example, a fragment of SEQ ID NO:1-24 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-24. The precise length of a fragment of SEQ ID NO:1-24 and the region of SEQ ID NO:1-24 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the

intended purpose for the fragment.

A "full length" polynucleotide sequence is one containing at least a translation initiation codon (e.g., methionine) followed by an open reading frame and a translation termination codon. A "full length" polynucleotide sequence encodes a "full length" polypeptide sequence.

5 "Homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

The terms "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in
10 the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of
15 molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent
20 similarity" between aligned polynucleotide sequences.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at
25 <http://www.ncbi.nlm.nih.gov/BLAST/>. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at <http://www.ncbi.nlm.nih.gov/gorf/bl2.html>. The
30 "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Reward for match: 1

Penalty for mismatch: -2

Open Gap: 5 and Extension Gap: 2 penalties

Gap x drop-off: 50

5 *Expect: 10*

Word Size: 11

Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example,
 10 over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

15 Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to
 20 the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

25 Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default
 30 residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.12 (April-21-2000) with blastp set at default parameters. Such default parameters may be, for

example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

5 *Expect: 10*

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

15 "Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size and which contain all of the elements required for chromosome replication, segregation and maintenance.

The term "humanized antibody" refers to an antibody molecule in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

20 "Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of complementarity. Specific hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity.

30 Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml sheared, denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Such wash temperatures are typically selected to be about

5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook, J. et al. (1989) 5 Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may 10 be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, sheared and denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily 15 apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A 20 hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide 25 sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

30 An "immunogenic fragment" is a polypeptide or oligopeptide fragment of PKIN which is capable of eliciting an immune response when introduced into a living organism, for example, a mammal. The term "immunogenic fragment" also includes any polypeptide or oligopeptide fragment of PKIN which is useful in any of the antibody production methods disclosed herein or known in the art.

The term "microarray" refers to an arrangement of a plurality of polynucleotides,

polypeptides, or other chemical compounds on a substrate.

The terms "element" and "array element" refer to a polynucleotide, polypeptide, or other chemical compound having a unique and defined position on a microarray.

The term "modulate" refers to a change in the activity of PKIN. For example, modulation
5 may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of PKIN.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the
10 antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with a second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Operably linked DNA sequences may be in close proximity or contiguous and, where
15 necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and
20 may be pegylated to extend their lifespan in the cell.

"Post-translational modification" of an PKIN may involve lipidation, glycosylation, phosphorylation, acetylation, racemization, proteolytic cleavage, and other modifications known in the art. These processes may occur synthetically or biochemically. Biochemical modifications will vary by cell type depending on the enzymatic milieu of PKIN.

25 "Probe" refers to nucleic acid sequences encoding PKIN, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target
30 polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also

be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

5 Methods for preparing and using probes and primers are described in the references, for example Sambrook, J. et al. (1989) Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel, F.M. et al. (1987) Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis, M. et al. (1990) PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs
10 can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

 Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to
15 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase
20 sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may
25 also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved
30 oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence. This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, *supra*. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be used to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

A "regulatory element" refers to a nucleic acid sequence usually derived from untranslated regions of a gene and includes enhancers, promoters, introns, and 5' and 3' untranslated regions (UTRs). Regulatory elements interact with host or viral proteins which control transcription, translation, or RNA stability.

"Reporter molecules" are chemical or biochemical moieties used for labeling a nucleic acid, amino acid, or antibody. Reporter molecules include radionuclides; enzymes; fluorescent, chemiluminescent, or chromogenic agents; substrates; cofactors; inhibitors; magnetic particles; and other moieties known in the art.

An "RNA equivalent," in reference to a DNA sequence, is composed of the same linear sequence of nucleotides as the reference DNA sequence with the exception that all occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The term "sample" is used in its broadest sense. A sample suspected of containing PKIN, nucleic acids encoding PKIN, or fragments thereof may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide comprising the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

5 A "substitution" refers to the replacement of one or more amino acid residues or nucleotides by different amino acid residues or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells,
10 trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

A "transcript image" refers to the collective pattern of gene expression by a particular cell type or tissue under given conditions at a given time.

"Transformation" describes a process by which exogenous DNA is introduced into a recipient cell. Transformation may occur under natural or artificial conditions according to various methods
15 well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected based on the type of host cell being transformed and may include, but is not limited to, bacteriophage or viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed cells" includes stably transformed cells in which the inserted DNA is capable of replication either as
20 an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "transgenic organism," as used herein, is any organism, including but not limited to animals and plants, in which one or more of the cells of the organism contains heterologous nucleic acid introduced by way of human intervention, such as by transgenic techniques well known in the art. The
25 nucleic acid is introduced into the cell, directly or indirectly by introduction into a precursor of the cell, by way of deliberate genetic manipulation, such as by microinjection or by infection with a recombinant virus. The term genetic manipulation does not include classical cross-breeding, or in vitro fertilization, but rather is directed to the introduction of a recombinant DNA molecule. The transgenic organisms contemplated in accordance with the present invention include bacteria, cyanobacteria,
30 fungi, plants and animals. The isolated DNA of the present invention can be introduced into the host by methods known in the art, for example infection, transfection, transformation or transconjugation. Techniques for transferring the DNA of the present invention into such organisms are widely known and provided in references such as Sambrook et al. (1989), supra.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having

at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides will generally have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human human kinases (PKIN), the polynucleotides encoding PKIN, and the use of these compositions for the diagnosis, treatment, or prevention of cancer, immune disorders, disorders affecting growth and development, cardiovascular diseases, and lipid disorders.

Table 1 summarizes the nomenclature for the full length polynucleotide and polypeptide sequences of the invention. Each polynucleotide and its corresponding polypeptide are correlated to a single Incyte project identification number (Incyte Project ID). Each polypeptide sequence is denoted by both a polypeptide sequence identification number (Polypeptide SEQ ID NO:) and an Incyte

polypeptide sequence number (Incyte Polypeptide ID) as shown. Each polynucleotide sequence is denoted by both a polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and an Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) as shown.

Table 2 shows sequences with homology to the polypeptides of the invention as identified by BLAST analysis against the GenBank protein (genpept) database. Columns 1 and 2 show the polypeptide sequence identification number (Polypeptide SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for polypeptides of the invention. Column 3 shows the GenBank identification number (Genbank ID NO:) of the nearest GenBank homolog. Column 4 shows the probability score for the match between each polypeptide and its GenBank homolog. Column 5 shows the annotation of the GenBank homolog along with relevant citations where applicable, all of which are expressly incorporated by reference herein.

Table 3 shows various structural features of the polypeptides of the invention. Columns 1 and 2 show the polypeptide sequence identification number (SEQ ID NO:) and the corresponding Incyte polypeptide sequence number (Incyte Polypeptide ID) for each polypeptide of the invention. Column 3 shows the number of amino acid residues in each polypeptide. Column 4 shows potential phosphorylation sites, and column 5 shows potential glycosylation sites, as determined by the MOTIFS program of the GCG sequence analysis software package (Genetics Computer Group, Madison WI). Column 6 shows amino acid residues comprising signature sequences, domains, and motifs. Column 7 shows analytical methods for protein structure/function analysis and in some cases, searchable databases to which the analytical methods were applied.

Together, Tables 2 and 3 summarize the properties of polypeptides of the invention, and these properties establish that the claimed polypeptides are human kinases. For example, SEQ ID NO:2 is 95% identical to rat myotonic dystrophy kinase-related Cdc42-binding kinase (GenBank ID g2736151) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:2 also contains kinase active site domains, a phorbol ester binding domain, and a protein-protein interaction domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) BLIMPS, MOTIFS, and PROFILESCAN analyses confirm the presence of these domains and provide further corroborative evidence that SEQ ID NO:2 is a protein kinase. In an alternate example, SEQ ID NO:4 is 79% identical to *Rattus norvegicus* extracellular signal-regulated kinase 7 (ERK7) (GenBank ID g4220888) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 5.3e-171, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. In another example,

SEQ ID NO:4 is 47% identical to *Leishmania mexicana* MAP-kinase homologue (LMPK) (GenBank ID g2131000) with a probability score of $4.2e-70$ as determined by the BLAST. (See Table 2.) It has been shown that *Leishmania mexicana* mutants, deleted for LMPK, lose the ability to cause a progressive disease in Balb/c mice. These *L. mexicana* mutants were restored to infectivity in

5 complementation experiments, demonstrating that LMPK is essential for the infectivity of *L. mexicana* in an infected host. Additionally, SEQ ID NO:4 is 48% identical to a MAP-kinase homologue from the human malaria parasite, *Plasmodium falciparum* (GenBank ID g1360110) with a probability score of $5.8e-73$ as determined by the BLAST. (See Table 2.) This homologue is closely related to MAP-kinases, which play important roles in eukaryotic adaptive response and signal transduction. SEQ ID

10 NO:4 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS reveals a tyrosine kinase catalytic domain signature (See Table 3.) Additional data from MOTIFS and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:4 is a protein kinase. SEQ ID NO:5 is 45% identical

15 to *Mus musculus* serine/threonine kinase (GenBank ID g404634) as determined by the BLAST. (See Table 2.) The BLAST probability score is $2.6e-54$. SEQ ID NO:5 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS_PRINTS reveals a tyrosine kinase catalytic domain signature. BLAST_DOMO data

20 indicates the presence of a protein kinase domain. Additional data from MOTIFS and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:5 is a protein kinase. In an alternate example, SEQ ID NO:7 is 53% identical to chicken qin-induced kinase (Qik), a serine-threonine kinase (GenBank ID g6760436) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is $9.2e-125$, which indicates the

25 probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:7 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:7 is a protein kinase. In an alternate example, SEQ ID NO:8

30 is 55% identical to human adenylate kinase (GenBank ID g5757703) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is 0.0, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:8 also contains a eukaryotic protein kinase domain and a PDZ domain, as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM

database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:8 is a protein kinase. In an alternate example, SEQ ID NO:16 is 42% identical to rat serine/threonine protein kinase (GenBank ID g4115429) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is $7.9e-53$, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:16 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:16 is a protein kinase. In an alternate example, SEQ ID NO:19 is 95% identical to rat nucleoside diphosphate kinase beta isoform (GenBank ID g286232) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is $3.1e-76$, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:19 also contains a nucleoside diphosphate kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:19 is a nucleoside diphosphate kinase. In an alternate example, SEQ ID NO:24 is 52% identical to murine apoptosis associated tyrosine kinase (GenBank ID g2459993) as determined by the Basic Local Alignment Search Tool (BLAST). (See Table 2.) The BLAST probability score is $1.5e-153$, which indicates the probability of obtaining the observed polypeptide sequence alignment by chance. SEQ ID NO:24 also contains a eukaryotic protein kinase domain as determined by searching for statistically significant matches in the hidden Markov model (HMM)-based PFAM database of conserved protein family domains. (See Table 3.) Data from BLIMPS, MOTIFS, and PROFILESCAN analyses provide further corroborative evidence that SEQ ID NO:24 is a tyrosine kinase. SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:6, SEQ ID NO:9-15, SEQ ID NO:17-18, and SEQ ID NO:20-23 were analyzed and annotated in a similar manner. The algorithms and parameters for the analysis of SEQ ID NO:1-24 are described in Table 7.

As shown in Table 4, the full length polynucleotide sequences of the present invention were assembled using cDNA sequences or coding (exon) sequences derived from genomic DNA, or any combination of these two types of sequences. Columns 1 and 2 list the polynucleotide sequence identification number (Polynucleotide SEQ ID NO:) and the corresponding Incyte polynucleotide consensus sequence number (Incyte Polynucleotide ID) for each polynucleotide of the invention. Column 3 shows the length of each polynucleotide sequence in basepairs. Column 4 lists fragments of

the polynucleotide sequences which are useful, for example, in hybridization or amplification technologies that identify SEQ ID NO:25-48 or that distinguish between SEQ ID NO:25-48 and related polynucleotide sequences. Column 5 shows identification numbers corresponding to cDNA sequences, coding sequences (exons) predicted from genomic DNA, and/or sequence assemblages comprised of both cDNA and genomic DNA. These sequences were used to assemble the full length polynucleotide sequences of the invention. Columns 6 and 7 of Table 4 show the nucleotide start (5') and stop (3') positions of the cDNA and/or genomic sequences in column 5 relative to their respective full length sequences.

The identification numbers in Column 5 of Table 4 may refer specifically, for example, to Incyte cDNAs along with their corresponding cDNA libraries. For example, 6259135F8 is the identification number of an Incyte cDNA sequence, and BMARTXT06 is the cDNA library from which it is derived. Incyte cDNAs for which cDNA libraries are not indicated were derived from pooled cDNA libraries (e.g., 71899371V1). Alternatively, the identification numbers in column 5 may refer to GenBank cDNAs or ESTs (e.g., g1441460) which contributed to the assembly of the full length polynucleotide sequences. In addition, the identification numbers in column 5 may identify sequences derived from the ENSEMBL (The Sanger Centre, Cambridge, UK) database (*i.e.*, those sequences including the designation "ENST"). Alternatively, the identification numbers in column 5 may be derived from the NCBI RefSeq Nucleotide Sequence Records Database (*i.e.*, those sequences including the designation "NM" or "NT") or the NCBI RefSeq Protein Sequence Records (*i.e.*, those sequences including the designation "NP"). Alternatively, the identification numbers in column 5 may refer to assemblages of both cDNA and Genscan-predicted exons brought together by an "exon stitching" algorithm. For example, FL_XXXXXX_N₁_N₂_YYYYY_N₃_N₄ represents a "stitched" sequence in which XXXXXX is the identification number of the cluster of sequences to which the algorithm was applied, and YYYYY is the number of the prediction generated by the algorithm, and N_{1,2,3...}, if present, represent specific exons that may have been manually edited during analysis (See Example V). Alternatively, the identification numbers in column 5 may refer to assemblages of exons brought together by an "exon-stretching" algorithm. For example, FLXXXXXX_gAAAAA_gBBBBB_1_N is the identification number of a "stretched" sequence, with XXXXXX being the Incyte project identification number, gAAAAA being the GenBank identification number of the human genomic sequence to which the "exon-stretching" algorithm was applied, gBBBBB being the GenBank identification number or NCBI RefSeq identification number of the nearest GenBank protein homolog, and N referring to specific exons (See Example V). In instances where a RefSeq sequence was used as a protein homolog for the "exon-stretching" algorithm, a

RefSeq identifier (denoted by "NM," "NP," or "NT") may be used in place of the GenBank identifier (i.e., gBBBBB).

Alternatively, a prefix identifies component sequences that were hand-edited, predicted from genomic DNA sequences, or derived from a combination of sequence analysis methods. The

- 5 following Table lists examples of component sequence prefixes and corresponding sequence analysis methods associated with the prefixes (see Example IV and Example V).

| Prefix | Type of analysis and/or examples of programs |
|----------------|---|
| GNN, GFG, ENST | Exon prediction from genomic sequences using, for example, GENSCAN (Stanford University, CA, USA) or FGENES (Computer Genomics Group, The Sanger Centre, Cambridge, UK). |
| 10 GBI | Hand-edited analysis of genomic sequences. |
| FL | Stitched or stretched genomic sequences (see Example V). |
| INCY | Full length transcript and exon prediction from mapping of EST sequences to the genome. Genomic location and EST composition data are combined to predict the exons and resulting transcript. |

In some cases, Incyte cDNA coverage redundant with the sequence coverage shown in
 15 column 5 was obtained to confirm the final consensus polynucleotide sequence, but the relevant Incyte cDNA identification numbers are not shown.

Table 5 shows the representative cDNA libraries for those full length polynucleotide sequences which were assembled using Incyte cDNA sequences. The representative cDNA library is the Incyte cDNA library which is most frequently represented by the Incyte cDNA sequences
 20 which were used to assemble and confirm the above polynucleotide sequences. The tissues and vectors which were used to construct the cDNA libraries shown in Table 5 are described in Table 6.

The invention also encompasses PKIN variants. A preferred PKIN variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the PKIN amino acid sequence, and which contains at least one functional or
 25 structural characteristic of PKIN.

The invention also encompasses polynucleotides which encode PKIN. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:25-48, which encodes PKIN. The polynucleotide sequences of SEQ ID NO:25-48, as presented in the Sequence Listing, embrace the equivalent RNA sequences,

wherein occurrences of the nitrogenous base thymine are replaced with uracil, and the sugar backbone is composed of ribose instead of deoxyribose.

The invention also encompasses a variant of a polynucleotide sequence encoding PKIN. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least
5 about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding PKIN. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:25-48 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ
10 ID NO:25-48. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of PKIN.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding PKIN, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus,
15 the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring PKIN, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode PKIN and its variants are generally capable of
20 hybridizing to the nucleotide sequence of the naturally occurring PKIN under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding PKIN or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which
25 particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding PKIN and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode PKIN and
30 PKIN derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding PKIN or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:25-48 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) *Methods Enzymol.* 152:399-407; Kimmel, A.R. (1987) *Methods Enzymol.* 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in 'Definitions.'

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Applied Biosystems), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Applied Biosystems). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Applied Biosystems), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding PKIN may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) *PCR Methods Applic.* 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) *Nucleic Acids Res.* 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al. (1991) *PCR Methods Applic.* 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) *Nucleic Acids Res.* 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo

Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 primer analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Applied Biosystems), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode PKIN may be cloned in recombinant DNA molecules that direct expression of PKIN, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express PKIN.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter PKIN-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

The nucleotides of the present invention may be subjected to DNA shuffling techniques such as MOLECULARBREEDING (Maxygen Inc., Santa Clara CA; described in U.S. Patent Number

5,837,458; Chang, C.-C. et al. (1999) *Nat. Biotechnol.* 17:793-797; Christians, F.C. et al. (1999) *Nat. Biotechnol.* 17:259-264; and Crameri, A. et al. (1996) *Nat. Biotechnol.* 14:315-319) to alter or improve the biological properties of PKIN, such as its biological or enzymatic activity or its ability to bind to other molecules or compounds. DNA shuffling is a process by which a library of gene variants is produced using PCR-mediated recombination of gene fragments. The library is then subjected to selection or screening procedures that identify those gene variants with the desired properties. These preferred variants may then be pooled and further subjected to recursive rounds of DNA shuffling and selection/screening. Thus, genetic diversity is created through "artificial" breeding and rapid molecular evolution. For example, fragments of a single gene containing random point mutations may be recombined, screened, and then reshuffled until the desired properties are optimized. Alternatively, fragments of a given gene may be recombined with fragments of homologous genes in the same gene family, either from the same or different species, thereby maximizing the genetic diversity of multiple naturally occurring genes in a directed and controllable manner.

In another embodiment, sequences encoding PKIN may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) *Nucleic Acids Symp. Ser.* 7:215-223; and Horn, T. et al. (1980) *Nucleic Acids Symp. Ser.* 7:225-232.) Alternatively, PKIN itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solution-phase or solid-phase techniques. (See, e.g., Creighton, T. (1984) *Proteins, Structures and Molecular Properties*, WH Freeman, New York NY, pp. 55-60; and Roberge, J.Y. et al. (1995) *Science* 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Applied Biosystems). Additionally, the amino acid sequence of PKIN, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide or a polypeptide having a sequence of a naturally occurring polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) *Methods Enzymol.* 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, *supra*, pp. 28-53.)

In order to express a biologically active PKIN, the nucleotide sequences encoding PKIN or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding PKIN. Such elements may vary in their strength and specificity. Specific initiation signals

may also be used to achieve more efficient translation of sequences encoding PKIN. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding PKIN and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) *Results Probl. Cell Differ.* 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding PKIN and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding PKIN. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. (See, e.g., Sambrook, supra; Ausubel, supra; Van Heeke, G. and S.M. Schuster (1989) *J. Biol. Chem.* 264:5503-5509; Engelhard, E.K. et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:3224-3227; Sandig, V. et al. (1996) *Hum. Gene Ther.* 7:1937-1945; Takamatsu, N. (1987) *EMBO J.* 6:307-311; The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196; Logan, J. and T. Shenk (1984) *Proc. Natl. Acad. Sci. USA* 81:3655-3659; and Harrington, J.J. et al. (1997) *Nat. Genet.* 15:345-355.) Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. (See, e.g., Di Nicola, M. et al. (1998) *Cancer Gen. Ther.* 5(6):350-356; Yu, M. et al. (1993) *Proc. Natl. Acad. Sci. USA* 90(13):6340-6344; Buller, R.M. et al. (1985) *Nature* 317(6040):813-815; McGregor, D.P. et al. (1994) *Mol. Immunol.* 31(3):219-226; and Verma, I.M. and N. Somia (1997) *Nature* 389:239-242.) The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding PKIN. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding PKIN can be achieved using a multifunctional *E. coli* vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPT11 plasmid (Life Technologies). Ligation of sequences encoding PKIN into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for *in vitro* transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of PKIN are needed, e.g. for the production of antibodies, vectors which direct high level expression of PKIN may be used. For example, vectors containing the strong, inducible SP6 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of PKIN. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast *Saccharomyces cerevisiae* or *Pichia pastoris*. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, *supra*; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of PKIN. Transcription of sequences encoding PKIN may be driven by viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al. (1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., *The McGraw Hill Yearbook of Science and Technology* (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding PKIN may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses PKIN in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma

virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are
5 constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of PKIN in cell lines is preferred. For example, sequences encoding PKIN can be transformed into cell
10 lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the
15 introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine
phosphoribosyltransferase genes, for use in *tk* and *ap^r* cells, respectively. (See, e.g., Wigler, M. et
20 al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g.,
Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981)
25 J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), β glucuronidase and its substrate β -glucuronide, or luciferase and its substrate
luciferin may be used. These markers can be used not only to identify transformants, but also to
30 quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding PKIN is inserted within a marker gene sequence, transformed cells containing

sequences encoding PKIN can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding PKIN under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

5 In general, host cells that contain the nucleic acid sequence encoding PKIN and that express PKIN may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

10 Immunological methods for detecting and measuring the expression of PKIN using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on PKIN is preferred, but a competitive
15 binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

20 A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding PKIN include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding PKIN, or any fragments thereof, may be cloned into a vector
25 for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for
30 ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding PKIN may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence

and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode PKIN may be designed to contain signal sequences which direct secretion of PKIN through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding PKIN may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric PKIN protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of PKIN activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the PKIN encoding sequence and the heterologous protein sequence, so that PKIN may be cleaved away from the heterologous moiety following purification. Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled PKIN may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ³⁵S-methionine.

PKIN of the present invention or fragments thereof may be used to screen for compounds that specifically bind to PKIN. At least one and up to a plurality of test compounds may be screened for specific binding to PKIN. Examples of test compounds include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

5 In one embodiment, the compound thus identified is closely related to the natural ligand of PKIN, e.g., a ligand or fragment thereof, a natural substrate, a structural or functional mimetic, or a natural binding partner. (See, e.g., Coligan, J.E. et al. (1991) Current Protocols in Immunology 1(2): Chapter 5.) Similarly, the compound can be closely related to the natural receptor to which PKIN binds, or to at least a fragment of the receptor, e.g., the ligand binding site. In either case, the
10 compound can be rationally designed using known techniques. In one embodiment, screening for these compounds involves producing appropriate cells which express PKIN, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, Drosophila, or E. coli. Cells expressing PKIN or cell membrane fractions which contain PKIN are then contacted with a test compound and binding, stimulation, or inhibition of activity of either PKIN or the compound is
15 analyzed.

An assay may simply test binding of a test compound to the polypeptide, wherein binding is detected by a fluorophore, radioisotope, enzyme conjugate, or other detectable label. For example, the assay may comprise the steps of combining at least one test compound with PKIN, either in solution or affixed to a solid support, and detecting the binding of PKIN to the compound. Alternatively, the
20 assay may detect or measure binding of a test compound in the presence of a labeled competitor. Additionally, the assay may be carried out using cell-free preparations, chemical libraries, or natural product mixtures, and the test compound(s) may be free in solution or affixed to a solid support.

PKIN of the present invention or fragments thereof may be used to screen for compounds that modulate the activity of PKIN. Such compounds may include agonists, antagonists, or partial or
25 inverse agonists. In one embodiment, an assay is performed under conditions permissive for PKIN activity, wherein PKIN is combined with at least one test compound, and the activity of PKIN in the presence of a test compound is compared with the activity of PKIN in the absence of the test compound. A change in the activity of PKIN in the presence of the test compound is indicative of a compound that modulates the activity of PKIN. Alternatively, a test compound is combined with an in
30 vitro or cell-free system comprising PKIN under conditions suitable for PKIN activity, and the assay is performed. In either of these assays, a test compound which modulates the activity of PKIN may do so indirectly and need not come in direct contact with the test compound. At least one and up to a plurality of test compounds may be screened.

In another embodiment, polynucleotides encoding PKIN or their mammalian homologs may be "knocked out" in an animal model system using homologous recombination in embryonic stem (ES) cells. Such techniques are well known in the art and are useful for the generation of animal models of human disease. (See, e.g., U.S. Patent Number 5,175,383 and U.S. Patent Number 5,767,337.) For example, mouse ES cells, such as the mouse 129/SvJ cell line, are derived from the early mouse embryo and grown in culture. The ES cells are transformed with a vector containing the gene of interest disrupted by a marker gene, e.g., the neomycin phosphotransferase gene (neo; Capecchi, M.R. (1989) Science 244:1288-1292). The vector integrates into the corresponding region of the host genome by homologous recombination. Alternatively, homologous recombination takes place using the Cre-loxP system to knockout a gene of interest in a tissue- or developmental stage-specific manner (Marth, J.D. (1996) Clin. Invest. 97:1999-2002; Wagner, K.U. et al. (1997) Nucleic Acids Res. 25:4323-4330). Transformed ES cells are identified and microinjected into mouse cell blastocysts such as those from the C57BL/6 mouse strain. The blastocysts are surgically transferred to pseudopregnant dams, and the resulting chimeric progeny are genotyped and bred to produce heterozygous or homozygous strains. Transgenic animals thus generated may be tested with potential therapeutic or toxic agents.

Polynucleotides encoding PKIN may also be manipulated in vitro in ES cells derived from human blastocysts. Human ES cells have the potential to differentiate into at least eight separate cell lineages including endoderm, mesoderm, and ectodermal cell types. These cell lineages differentiate into, for example, neural cells, hematopoietic lineages, and cardiomyocytes (Thomson, J.A. et al. (1998) Science 282:1145-1147).

Polynucleotides encoding PKIN can also be used to create "knockin" humanized animals (pigs) or transgenic animals (mice or rats) to model human disease. With knockin technology, a region of a polynucleotide encoding PKIN is injected into animal ES cells, and the injected sequence integrates into the animal cell genome. Transformed cells are injected into blastulae, and the blastulae are implanted as described above. Transgenic progeny or inbred lines are studied and treated with potential pharmaceutical agents to obtain information on treatment of a human disease. Alternatively, a mammal inbred to overexpress PKIN, e.g., by secreting PKIN in its milk, may also serve as a convenient source of that protein (Janne, J. et al. (1998) Biotechnol. Annu. Rev. 4:55-74).

30 THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of PKIN and human kinases. In addition, the expression of PKIN is closely associated with neurological, brain, immune system, diseased, developing, myometrium, smooth muscle cell, thyroid, nervous, reproductive, lung, gastrointestinal, developmental, tumorous, and cardiac tissues. Therefore,

PKIN appears to play a role in cancer, immune disorders, disorders affecting growth and development, cardiovascular diseases, and lipid disorders. In the treatment of disorders associated with increased PKIN expression or activity, it is desirable to decrease the expression or activity of PKIN. In the treatment of disorders associated with decreased PKIN expression or activity, it is
 5 desirable to increase the expression or activity of PKIN.

Therefore, in one embodiment, PKIN or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PKIN. Examples of such disorders include, but are not limited to, a cancer, such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of
 10 the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus, leukemias such as multiple myeloma and lymphomas such as Hodgkin's disease; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing
 15 spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's
 20 thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, viral,
 25 bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a growth and developmental disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in
 30 particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus, renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental

retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Sydenham's chorea and cerebral palsy, spina bifida, anencephaly, craniorachischisis, congenital glaucoma, cataract, and

5 sensorineural hearing loss; a cardiovascular disease, such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, and complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris, myocardial infarction, hypertensive heart disease,

10 degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of cardiac transplantation, congenital lung

15 anomalies, atelectasis, pulmonary congestion and edema, pulmonary embolism, pulmonary hemorrhage, pulmonary infarction, pulmonary hypertension, vascular sclerosis, obstructive pulmonary disease, restrictive pulmonary disease, chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchial asthma, bronchiectasis, bacterial pneumonia, viral and mycoplasmal pneumonia, lung abscess, pulmonary tuberculosis, diffuse interstitial diseases, pneumoconioses, sarcoidosis, idiopathic

20 pulmonary fibrosis, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary eosinophilia bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary hemorrhage syndromes, Goodpasture's syndromes, idiopathic pulmonary hemosiderosis, pulmonary involvement in collagen-vascular disorders, pulmonary alveolar proteinosis, lung tumors, inflammatory and noninflammatory pleural effusions, pneumothorax, pleural tumors, drug-induced lung disease, radiation

25 induced lung disease, and complications of lung transplantation; and a lipid disorder such as fatty liver, cholestasis, primary biliary cirrhosis, carnitine deficiency, carnitine palmitoyltransferase deficiency, myoadenylate deaminase deficiency, hypertriglyceridemia, lipid storage disorders such as Fabry's disease, Gaucher's disease, Niemann-Pick's disease, metachromatic leukodystrophy, adrenoleukodystrophy, GM₂ gangliosidosis, and ceroid lipofuscinosis, abetalipoproteinemia, Tangier

30 disease, hyperlipoproteinemia, diabetes mellitus, lipodystrophy, lipomatosis, acute panniculitis, disseminated fat necrosis, adiposis dolorosa, lipid adrenal hyperplasia, minimal change disease, lipomas, atherosclerosis, hypercholesterolemia, hypercholesterolemia with hypertriglyceridemia, primary hypoalphalipoproteinemia, hypothyroidism, renal disease, liver disease, lecithin:cholesterol

acyltransferase deficiency, cerebrotendinous xanthomatosis, sitosterolemia, hypocholesterolemia, Tay-Sachs disease, Sandhoff's disease, hyperlipidemia, hyperlipemia, lipid myopathies, and obesity.

In another embodiment, a vector capable of expressing PKIN or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased
5 expression or activity of PKIN including, but not limited to, those described above.

In a further embodiment, a composition comprising a substantially purified PKIN in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PKIN including, but not limited to, those provided above.

10 In still another embodiment, an agonist which modulates the activity of PKIN may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of PKIN including, but not limited to, those listed above.

In a further embodiment, an antagonist of PKIN may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PKIN. Examples of such
15 disorders include, but are not limited to, those cancer, immune disorders, disorders affecting growth and development, cardiovascular diseases, and lipid disorders described above. In one aspect, an antibody which specifically binds PKIN may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express PKIN.

20 In an additional embodiment, a vector expressing the complement of the polynucleotide encoding PKIN may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of PKIN including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate
25 therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

30 An antagonist of PKIN may be produced using methods which are generally known in the art. In particular, purified PKIN may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind PKIN. Antibodies to PKIN may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments

produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with PKIN or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to PKIN have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein. Short stretches of PKIN amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to PKIN may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce PKIN-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for PKIN may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the $F(ab')_2$ fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D. et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between PKIN and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering PKIN epitopes is generally used, but a competitive binding assay may also be employed (Pound, *supra*).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for PKIN. Affinity is expressed as an association constant, K_a , which is defined as the molar concentration of PKIN-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple PKIN epitopes, represents the average affinity, or avidity, of the antibodies for PKIN. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular PKIN epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the PKIN-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of PKIN, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington DC; Liddell, J.E. and A. Cryer (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of PKIN-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for

antibody quality and usage in various applications, are generally available. (See, e.g., Catty, *supra*, and Coligan et al. *supra*.)

In another embodiment of the invention, the polynucleotides encoding PKIN, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, modifications of gene expression can be achieved by designing complementary sequences or antisense molecules (DNA, RNA, PNA, or modified oligonucleotides) to the coding or regulatory regions of the gene encoding PKIN. Such technology is well known in the art, and antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding PKIN. (See, e.g., Agrawal, S., ed. (1996) *Antisense Therapeutics*, Humana Press Inc., Totawa NJ.)

In therapeutic use, any gene delivery system suitable for introduction of the antisense sequences into appropriate target cells can be used. Antisense sequences can be delivered intracellularly in the form of an expression plasmid which, upon transcription, produces a sequence complementary to at least a portion of the cellular sequence encoding the target protein. (See, e.g., Slater, J.E. et al. (1998) *J. Allergy Clin. Immunol.* 102(3):469-475; and Scanlon, K.J. et al. (1995) 9(13):1288-1296.) Antisense sequences can also be introduced intracellularly through the use of viral vectors, such as retrovirus and adeno-associated virus vectors. (See, e.g., Miller, A.D. (1990) *Blood* 76:271; Ausubel, *supra*; Uckert, W. and W. Walther (1994) *Pharmacol. Ther.* 63(3):323-347.) Other gene delivery mechanisms include liposome-derived systems, artificial viral envelopes, and other systems known in the art. (See, e.g., Rossi, J.J. (1995) *Br. Med. Bull.* 51(1):217-225; Boado, R.J. et al. (1998) *J. Pharm. Sci.* 87(11):1308-1315; and Morris, M.C. et al. (1997) *Nucleic Acids Res.* 25(14):2730-2736.)

In another embodiment of the invention, polynucleotides encoding PKIN may be used for somatic or germline gene therapy. Gene therapy may be performed to (i) correct a genetic deficiency (e.g., in the cases of severe combined immunodeficiency (SCID)-X1 disease characterized by X-linked inheritance (Cavazzana-Calvo, M. et al. (2000) *Science* 288:669-672), severe combined immunodeficiency syndrome associated with an inherited adenosine deaminase (ADA) deficiency (Blaese, R.M. et al. (1995) *Science* 270:475-480; Bordignon, C. et al. (1995) *Science* 270:470-475), cystic fibrosis (Zabner, J. et al. (1993) *Cell* 75:207-216; Crystal, R.G. et al. (1995) *Hum. Gene Therapy* 6:643-666; Crystal, R.G. et al. (1995) *Hum. Gene Therapy* 6:667-703), thalassemias, familial hypercholesterolemia, and hemophilia resulting from Factor VIII or Factor IX deficiencies (Crystal, R.G. (1995) *Science* 270:404-410; Verma, I.M. and N. Somia (1997) *Nature* 389:239-242)), (ii) express a conditionally lethal gene product (e.g., in the case of cancers which result from unregulated cell proliferation), or (iii) express a protein which affords protection against intracellular parasites (e.g., against human retroviruses, such as human immunodeficiency virus (HIV) (Baltimore, D. (1988)

Nature 335:395-396; Poeschla, E. et al. (1996) Proc. Natl. Acad. Sci. USA. 93:11395-11399), hepatitis B or C virus (HBV, HCV); fungal parasites, such as Candida albicans and Paracoccidioides brasiliensis; and protozoan parasites such as Plasmodium falciparum and Trypanosoma cruzi). In the case where a genetic deficiency in PKIN expression or regulation causes disease, the expression of

5 PKIN from an appropriate population of transduced cells may alleviate the clinical manifestations caused by the genetic deficiency.

In a further embodiment of the invention, diseases or disorders caused by deficiencies in PKIN are treated by constructing mammalian expression vectors encoding PKIN and introducing these vectors by mechanical means into PKIN-deficient cells. Mechanical transfer technologies for

10 use with cells in vivo or ex vitro include (i) direct DNA microinjection into individual cells, (ii) ballistic gold particle delivery, (iii) liposome-mediated transfection, (iv) receptor-mediated gene transfer, and (v) the use of DNA transposons (Morgan, R.A. and W.F. Anderson (1993) Annu. Rev. Biochem. 62:191-217; Ivics, Z. (1997) Cell 91:501-510; Boulay, J-L. and H. Récipon (1998) Curr. Opin. Biotechnol. 9:445-450).

15 Expression vectors that may be effective for the expression of PKIN include, but are not limited to, the PCDNA 3.1, EPITAG, PRCCMV2, PREP, PVAX, PCR2-TOPOTA vectors (Invitrogen, Carlsbad CA), PCMV-SCRIPT, PCMV-TAG, PEGSH/PERV (Stratagene, La Jolla CA), and PTET-OFF, PTET-ON, PTRE2, PTRE2-LUC, PTK-HYG (Clontech, Palo Alto CA). PKIN may be expressed using (i) a constitutively active promoter, (e.g., from cytomegalovirus (CMV), Rous

20 sarcoma virus (RSV), SV40 virus, thymidine kinase (TK), or β -actin genes), (ii) an inducible promoter (e.g., the tetracycline-regulated promoter (Gossen, M. and H. Bujard (1992) Proc. Natl. Acad. Sci. USA 89:5547-5551; Gossen, M. et al. (1995) Science 268:1766-1769; Rossi, F.M.V. and H.M. Blau (1998) Curr. Opin. Biotechnol. 9:451-456), commercially available in the T-REX plasmid (Invitrogen)); the ecdysone-inducible promoter (available in the plasmids PVGRXR and PIND; Invitrogen); the

25 FK506/rapamycin inducible promoter; or the RU486/mifepristone inducible promoter (Rossi, F.M.V. and Blau, H.M. supra), or (iii) a tissue-specific promoter or the native promoter of the endogenous gene encoding PKIN from a normal individual.

Commercially available liposome transformation kits (e.g., the PERFECT LIPID TRANSFECTION KIT, available from Invitrogen) allow one with ordinary skill in the art to deliver

30 polynucleotides to target cells in culture and require minimal effort to optimize experimental parameters. In the alternative, transformation is performed using the calcium phosphate method (Graham, F.L. and A.J. Eb (1973) Virology 52:456-467), or by electroporation (Neumann, E. et al. (1982) EMBO J. 1:841-845). The introduction of DNA to primary cells requires modification of these standardized mammalian transfection protocols.

In another embodiment of the invention, diseases or disorders caused by genetic defects with respect to PKIN expression are treated by constructing a retrovirus vector consisting of (i) the polynucleotide encoding PKIN under the control of an independent promoter or the retrovirus long terminal repeat (LTR) promoter, (ii) appropriate RNA packaging signals, and (iii) a Rev-responsive element (RRE) along with additional retrovirus *cis*-acting RNA sequences and coding sequences required for efficient vector propagation. Retrovirus vectors (e.g., PFB and PFBNEO) are commercially available (Stratagene) and are based on published data (Riviere, I. et al. (1995) Proc. Natl. Acad. Sci. USA 92:6733-6737), incorporated by reference herein. The vector is propagated in an appropriate vector producing cell line (VPCL) that expresses an envelope gene with a tropism for receptors on the target cells or a promiscuous envelope protein such as VSVg (Armentano, D. et al. (1987) J. Virol. 61:1647-1650; Bender, M.A. et al. (1987) J. Virol. 61:1639-1646; Adam, M.A. and A.D. Miller (1988) J. Virol. 62:3802-3806; Dull, T. et al. (1998) J. Virol. 72:8463-8471; Zufferey, R. et al. (1998) J. Virol. 72:9873-9880). U.S. Patent Number 5,910,434 to Rigg ("Method for obtaining retrovirus packaging cell lines producing high transducing efficiency retroviral supernatant") discloses a method for obtaining retrovirus packaging cell lines and is hereby incorporated by reference. Propagation of retrovirus vectors, transduction of a population of cells (e.g., CD4⁺ T-cells), and the return of transduced cells to a patient are procedures well known to persons skilled in the art of gene therapy and have been well documented (Ranga, U. et al. (1997) J. Virol. 71:7020-7029; Bauer, G. et al. (1997) Blood 89:2259-2267; Bonyhadi, M.L. (1997) J. Virol. 71:4707-4716; Ranga, U. et al. (1998) Proc. Natl. Acad. Sci. USA 95:1201-1206; Su, L. (1997) Blood 89:2283-2290).

In the alternative, an adenovirus-based gene therapy delivery system is used to deliver polynucleotides encoding PKIN to cells which have one or more genetic abnormalities with respect to the expression of PKIN. The construction and packaging of adenovirus-based vectors are well known to those with ordinary skill in the art. Replication defective adenovirus vectors have proven to be versatile for importing genes encoding immunoregulatory proteins into intact islets in the pancreas (Csete, M.E. et al. (1995) Transplantation 27:263-268). Potentially useful adenoviral vectors are described in U.S. Patent Number 5,707,618 to Armentano ("Adenovirus vectors for gene therapy"), hereby incorporated by reference. For adenoviral vectors, see also Antinozzi, P.A. et al. (1999) Annu. Rev. Nutr. 19:511-544 and Verma, I.M. and N. Somia (1997) Nature 389:239-242, both incorporated by reference herein.

In another alternative, a herpes-based, gene therapy delivery system is used to deliver polynucleotides encoding PKIN to target cells which have one or more genetic abnormalities with respect to the expression of PKIN. The use of herpes simplex virus (HSV)-based vectors may be especially valuable for introducing PKIN to cells of the central nervous system, for which HSV has a

tropism. The construction and packaging of herpes-based vectors are well known to those with ordinary skill in the art. A replication-competent herpes simplex virus (HSV) type 1-based vector has been used to deliver a reporter gene to the eyes of primates (Liu, X. et al. (1999) *Exp. Eye Res.* 169:385-395). The construction of a HSV-1 virus vector has also been disclosed in detail in U.S. Patent Number 5,804,413 to DeLuca ("Herpes simplex virus strains for gene transfer"), which is hereby incorporated by reference. U.S. Patent Number 5,804,413 teaches the use of recombinant HSV d92 which consists of a genome containing at least one exogenous gene to be transferred to a cell under the control of the appropriate promoter for purposes including human gene therapy. Also taught by this patent are the construction and use of recombinant HSV strains deleted for ICP4, ICP27 and ICP22. For HSV vectors, see also Goins, W.F. et al. (1999) *J. Virol.* 73:519-532 and Xu, H. et al. (1994) *Dev. Biol.* 163:152-161, hereby incorporated by reference. The manipulation of cloned herpesvirus sequences, the generation of recombinant virus following the transfection of multiple plasmids containing different segments of the large herpesvirus genomes, the growth and propagation of herpesvirus, and the infection of cells with herpesvirus are techniques well known to those of ordinary skill in the art.

In another alternative, an alphavirus (positive, single-stranded RNA virus) vector is used to deliver polynucleotides encoding PKIN to target cells. The biology of the prototypic alphavirus, Semliki Forest Virus (SFV), has been studied extensively and gene transfer vectors have been based on the SFV genome (Garoff, H. and K.-J. Li (1998) *Curr. Opin. Biotechnol.* 9:464-469). During alphavirus RNA replication, a subgenomic RNA is generated that normally encodes the viral capsid proteins. This subgenomic RNA replicates to higher levels than the full length genomic RNA, resulting in the overproduction of capsid proteins relative to the viral proteins with enzymatic activity (e.g., protease and polymerase). Similarly, inserting the coding sequence for PKIN into the alphavirus genome in place of the capsid-coding region results in the production of a large number of PKIN-coding RNAs and the synthesis of high levels of PKIN in vector transduced cells. While alphavirus infection is typically associated with cell lysis within a few days, the ability to establish a persistent infection in hamster normal kidney cells (BHK-21) with a variant of Sindbis virus (SIN) indicates that the lytic replication of alphaviruses can be altered to suit the needs of the gene therapy application (Dryga, S.A. et al. (1997) *Virology* 228:74-83). The wide host range of alphaviruses will allow the introduction of PKIN into a variety of cell types. The specific transduction of a subset of cells in a population may require the sorting of cells prior to transduction. The methods of manipulating infectious cDNA clones of alphaviruses, performing alphavirus cDNA and RNA transfections, and performing alphavirus infections, are well known to those with ordinary skill in the art.

Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may also be employed to inhibit gene expression. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases,

5 transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

10 Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding PKIN.

15 Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides, corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

20 Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding PKIN. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

30 RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine,

and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

An additional embodiment of the invention encompasses a method for screening for a compound which is effective in altering expression of a polynucleotide encoding PKIN. Compounds which may be effective in altering expression of a specific polynucleotide may include, but are not limited to, oligonucleotides, antisense oligonucleotides, triple helix-forming oligonucleotides, transcription factors and other polypeptide transcriptional regulators, and non-macromolecular chemical entities which are capable of interacting with specific polynucleotide sequences. Effective compounds may alter polynucleotide expression by acting as either inhibitors or promoters of polynucleotide expression. Thus, in the treatment of disorders associated with increased PKIN expression or activity, a compound which specifically inhibits expression of the polynucleotide encoding PKIN may be therapeutically useful, and in the treatment of disorders associated with decreased PKIN expression or activity, a compound which specifically promotes expression of the polynucleotide encoding PKIN may be therapeutically useful.

At least one, and up to a plurality, of test compounds may be screened for effectiveness in altering expression of a specific polynucleotide. A test compound may be obtained by any method commonly known in the art, including chemical modification of a compound known to be effective in altering polynucleotide expression; selection from an existing, commercially-available or proprietary library of naturally-occurring or non-natural chemical compounds; rational design of a compound based on chemical and/or structural properties of the target polynucleotide; and selection from a library of chemical compounds created combinatorially or randomly. A sample comprising a polynucleotide encoding PKIN is exposed to at least one test compound thus obtained. The sample may comprise, for example, an intact or permeabilized cell, or an *in vitro* cell-free or reconstituted biochemical system. Alterations in the expression of a polynucleotide encoding PKIN are assayed by any method commonly known in the art. Typically, the expression of a specific nucleotide is detected by hybridization with a probe having a nucleotide sequence complementary to the sequence of the polynucleotide encoding PKIN. The amount of hybridization may be quantified, thus forming the basis for a comparison of the expression of the polynucleotide both with and without exposure to one or more test compounds. Detection of a change in the expression of a polynucleotide exposed to a test compound indicates that the test compound is effective in altering the expression of the polynucleotide. A screen for a compound effective in altering expression of a specific polynucleotide can be carried out, for example, using a *Schizosaccharomyces pombe* gene expression system (Atkins, D. et al. (1999) U.S. Patent No. 5,932,435; Arndt, G.M. et al. (2000) Nucleic Acids Res. 28:E15) or a human cell line such as HeLa cell (Clarke, M.L. et al. (2000) Biochem. Biophys. Res. Commun.

268:8-13). A particular embodiment of the present invention involves screening a combinatorial library of oligonucleotides (such as deoxyribonucleotides, ribonucleotides, peptide nucleic acids, and modified oligonucleotides) for antisense activity against a specific polynucleotide sequence (Bruice, T.W. et al. (1997) U.S. Patent No. 5,686,242; Bruice, T.W. et al. (2000) U.S. Patent No. 6,022,691).

5 Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat.
10 Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a composition which
15 generally comprises an active ingredient formulated with a pharmaceutically acceptable excipient. Excipients may include, for example, sugars, starches, celluloses, gums, and proteins. Various formulations are commonly known and are thoroughly discussed in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA). Such compositions may consist of PKIN, antibodies to PKIN, and mimetics, agonists, antagonists, or inhibitors of PKIN.

20 The compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, pulmonary, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

Compositions for pulmonary administration may be prepared in liquid or dry powder form.
25 These compositions are generally aerosolized immediately prior to inhalation by the patient. In the case of small molecules (e.g. traditional low molecular weight organic drugs), aerosol delivery of fast-acting formulations is well-known in the art. In the case of macromolecules (e.g. larger peptides and proteins), recent developments in the field of pulmonary delivery via the alveolar region of the lung have enabled the practical delivery of drugs such as insulin to blood circulation (see, e.g., Patton, J.S.
30 et al., U.S. Patent No. 5,997,848). Pulmonary delivery has the advantage of administration without needle injection, and obviates the need for potentially toxic penetration enhancers.

Compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

Specialized forms of compositions may be prepared for direct intracellular delivery of macromolecules comprising PKIN or fragments thereof. For example, liposome preparations containing a cell-impermeable macromolecule may promote cell fusion and intracellular delivery of the macromolecule. Alternatively, PKIN or a fragment thereof may be joined to a short cationic N-terminal portion from the HIV Tat-1 protein. Fusion proteins thus generated have been found to transduce into the cells of all tissues, including the brain, in a mouse model system (Schwarze, S.R. et al. (1999) Science 285:1569-1572).

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, monkeys, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example PKIN or fragments thereof, antibodies of PKIN, and agonists, antagonists or inhibitors of PKIN, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg , up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art.

Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

5 In another embodiment, antibodies which specifically bind PKIN may be used for the diagnosis of disorders characterized by expression of PKIN, or in assays to monitor patients being treated with PKIN or agonists, antagonists, or inhibitors of PKIN. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for PKIN include methods which utilize the antibody and a label to detect PKIN in human body
10 fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring PKIN, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of PKIN expression. Normal
15 or standard values for PKIN expression are established by combining body fluids or cell extracts taken from normal mammalian subjects, for example, human subjects, with antibodies to PKIN under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of PKIN expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation
20 between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding PKIN may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of PKIN may be correlated with
25 disease. The diagnostic assay may be used to determine absence, presence, and excess expression of PKIN, and to monitor regulation of PKIN levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding PKIN or closely related molecules may be used to identify nucleic acid sequences which encode PKIN. The specificity of the probe, whether it is made
30 from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding PKIN, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the PKIN encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:25-48 or from genomic sequences including promoters, enhancers, and introns of the PKIN gene.

5 Means for producing specific hybridization probes for DNAs encoding PKIN include the cloning of polynucleotide sequences encoding PKIN or PKIN derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a
10 variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S , or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding PKIN may be used for the diagnosis of disorders associated with expression of PKIN. Examples of such disorders include, but are not limited to, a cancer, such as adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma,
15 teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus, leukemias such as multiple myeloma and lymphomas such as Hodgkin's disease; an immune disorder, such as acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress
20 syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), bronchitis, cholecystitis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, episodic lymphopenia with lymphocytotoxins, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's
25 syndrome, gout, Graves' disease, Hashimoto's thyroiditis, hypereosinophilia, irritable bowel syndrome, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer,
30 hemodialysis, and extracorporeal circulation, viral, bacterial, fungal, parasitic, protozoal, and helminthic infections, and trauma; a growth and developmental disorder, such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma,

teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus, renal tubular acidosis, anemia, Cushing's syndrome, achondroplastic dwarfism, Duchenne and Becker

5 muscular dystrophy, epilepsy, gonadal dysgenesis, WAGR syndrome (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), Smith-Magenis syndrome, myelodysplastic syndrome, hereditary mucoepithelial dysplasia, hereditary keratodermas, hereditary neuropathies such as Charcot-Marie-Tooth disease and neurofibromatosis, hypothyroidism, hydrocephalus, seizure disorders such as Sydenham's chorea and cerebral palsy, spina bifida, anencephaly,

10 craniorachischisis, congenital glaucoma, cataract, and sensorineural hearing loss; a cardiovascular disease, such as arteriovenous fistula, atherosclerosis, hypertension, vasculitis, Raynaud's disease, aneurysms, arterial dissections, varicose veins, thrombophlebitis and phlebothrombosis, vascular tumors, and complications of thrombolysis, balloon angioplasty, vascular replacement, and coronary artery bypass graft surgery, congestive heart failure, ischemic heart disease, angina pectoris,

15 myocardial infarction, hypertensive heart disease, degenerative valvular heart disease, calcific aortic valve stenosis, congenitally bicuspid aortic valve, mitral annular calcification, mitral valve prolapse, rheumatic fever and rheumatic heart disease, infective endocarditis, nonbacterial thrombotic endocarditis, endocarditis of systemic lupus erythematosus, carcinoid heart disease, cardiomyopathy, myocarditis, pericarditis, neoplastic heart disease, congenital heart disease, and complications of

20 cardiac transplantation, congenital lung anomalies, atelectasis, pulmonary congestion and edema, pulmonary embolism, pulmonary hemorrhage, pulmonary infarction, pulmonary hypertension, vascular sclerosis, obstructive pulmonary disease, restrictive pulmonary disease, chronic obstructive pulmonary disease, emphysema, chronic bronchitis, bronchial asthma, bronchiectasis, bacterial pneumonia, viral and mycoplasmal pneumonia, lung abscess, pulmonary tuberculosis, diffuse interstitial diseases,

25 pneumoconioses, sarcoidosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonitis, hypersensitivity pneumonitis, pulmonary eosinophilia bronchiolitis obliterans-organizing pneumonia, diffuse pulmonary hemorrhage syndromes, Goodpasture's syndromes, idiopathic pulmonary hemosiderosis, pulmonary involvement in collagen-vascular disorders, pulmonary alveolar proteinosis, lung tumors, inflammatory and noninflammatory pleural effusions, pneumothorax, pleural tumors, drug

30 induced lung disease, radiation-induced lung disease, and complications of lung transplantation; and a lipid disorder such as fatty liver, cholestasis, primary biliary cirrhosis, carnitine deficiency, carnitine palmitoyltransferase deficiency, myoadenylate deaminase deficiency, hypertriglyceridemia, lipid storage disorders such as Fabry's disease, Gaucher's disease, Niemann-Pick's disease, metachromatic leukodystrophy, adrenoleukodystrophy, GM₂ gangliosidosis, and ceroid lipofuscinosis,

abetalipoproteinemia, Tangier disease, hyperlipoproteinemia, diabetes mellitus, lipodystrophy, lipomatosis, acute panniculitis, disseminated fat necrosis, adiposis dolorosa, lipoid adrenal hyperplasia, minimal change disease, lipomas, atherosclerosis, hypercholesterolemia, hypercholesterolemia with hypertriglyceridemia, primary hypoalphalipoproteinemia, hypothyroidism, renal disease, liver disease, lecithin:cholesterol acyltransferase deficiency, cerebrotendinous xanthomatosis, sitosterolemia, hypocholesterolemia, Tay-Sachs disease, Sandhoff's disease, hyperlipidemia, hyperlipemia, lipid myopathies, and obesity. The polynucleotide sequences encoding PKIN may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered PKIN expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding PKIN may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding PKIN may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding PKIN in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of PKIN, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding PKIN, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding PKIN may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding PKIN, or a fragment of a polynucleotide complementary to the polynucleotide encoding PKIN, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

In a particular aspect, oligonucleotide primers derived from the polynucleotide sequences encoding PKIN may be used to detect single nucleotide polymorphisms (SNPs). SNPs are substitutions, insertions and deletions that are a frequent cause of inherited or acquired genetic disease in humans. Methods of SNP detection include, but are not limited to, single-stranded conformation polymorphism (SSCP) and fluorescent SSCP (fSSCP) methods. In SSCP, oligonucleotide primers derived from the polynucleotide sequences encoding PKIN are used to amplify DNA using the polymerase chain reaction (PCR). The DNA may be derived, for example, from diseased or normal tissue, biopsy samples, bodily fluids, and the like. SNPs in the DNA cause differences in the secondary and tertiary structures of PCR products in single-stranded form, and these differences are detectable using gel electrophoresis in non-denaturing gels. In fSSCP, the oligonucleotide primers are fluorescently labeled, which allows detection of the amplimers in high-throughput equipment such as DNA sequencing machines. Additionally, sequence database analysis methods, termed *in silico* SNP (isSNP), are capable of identifying polymorphisms by comparing the sequence of individual overlapping DNA fragments which assemble into a common consensus sequence. These computer-based methods filter out sequence variations due to laboratory preparation of DNA and sequencing errors using statistical models and automated analyses of DNA sequence chromatograms. In the alternative, SNPs may be detected and characterized by mass spectrometry using, for example, the high throughput MASSARRAY system (Sequenom, Inc., San Diego CA).

Methods which may also be used to quantify the expression of PKIN include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C.

et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer or polynucleotide of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

5 In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as elements on a microarray. The microarray can be used in transcript imaging techniques which monitor the relative expression levels of large numbers of genes simultaneously as described below. The microarray may also be used to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene
10 function, to understand the genetic basis of a disorder, to diagnose a disorder, to monitor progression/regression of disease as a function of gene expression, and to develop and monitor the activities of therapeutic agents in the treatment of disease. In particular, this information may be used to develop a pharmacogenomic profile of a patient in order to select the most appropriate and effective treatment regimen for that patient. For example, therapeutic agents which are highly effective and
15 display the fewest side effects may be selected for a patient based on his/her pharmacogenomic profile.

In another embodiment, PKIN, fragments of PKIN, or antibodies specific for PKIN may be used as elements on a microarray. The microarray may be used to monitor or measure protein-protein interactions, drug-target interactions, and gene expression profiles, as described above.

20 A particular embodiment relates to the use of the polynucleotides of the present invention to generate a transcript image of a tissue or cell type. A transcript image represents the global pattern of gene expression by a particular tissue or cell type. Global gene expression patterns are analyzed by quantifying the number of expressed genes and their relative abundance under given conditions and at a given time. (See Seilhamer et al., "Comparative Gene Transcript Analysis," U.S. Patent Number
25 5,840,484, expressly incorporated by reference herein.) Thus a transcript image may be generated by hybridizing the polynucleotides of the present invention or their complements to the totality of transcripts or reverse transcripts of a particular tissue or cell type. In one embodiment, the hybridization takes place in high-throughput format, wherein the polynucleotides of the present invention or their complements comprise a subset of a plurality of elements on a microarray. The
30 resultant transcript image would provide a profile of gene activity.

Transcript images may be generated using transcripts isolated from tissues, cell lines, biopsies, or other biological samples. The transcript image may thus reflect gene expression in vivo, as in the case of a tissue or biopsy sample, or in vitro, as in the case of a cell line.

Transcript images which profile the expression of the polynucleotides of the present invention may also be used in conjunction with in vitro model systems and preclinical evaluation of pharmaceuticals, as well as toxicological testing of industrial and naturally-occurring environmental compounds. All compounds induce characteristic gene expression patterns, frequently termed

5 molecular fingerprints or toxicant signatures, which are indicative of mechanisms of action and toxicity (Nuwaysir, E.F. et al. (1999) Mol. Carcinog. 24:153-159; Steiner, S. and N.L. Anderson (2000) Toxicol. Lett. 112-113:467-471, expressly incorporated by reference herein). If a test compound has a signature similar to that of a compound with known toxicity, it is likely to share those toxic properties. These fingerprints or signatures are most useful and refined when they contain expression information

10 from a large number of genes and gene families. Ideally, a genome-wide measurement of expression provides the highest quality signature. Even genes whose expression is not altered by any tested compounds are important as well, as the levels of expression of these genes are used to normalize the rest of the expression data. The normalization procedure is useful for comparison of expression data after treatment with different compounds. While the assignment of gene function to elements of a

15 toxicant signature aids in interpretation of toxicity mechanisms, knowledge of gene function is not necessary for the statistical matching of signatures which leads to prediction of toxicity. (See, for example, Press Release 00-02 from the National Institute of Environmental Health Sciences, released February 29, 2000, available at <http://www.niehs.nih.gov/oc/news/toxchip.htm>.) Therefore, it is important and desirable in toxicological screening using toxicant signatures to include all expressed

20 gene sequences.

In one embodiment, the toxicity of a test compound is assessed by treating a biological sample containing nucleic acids with the test compound. Nucleic acids that are expressed in the treated biological sample are hybridized with one or more probes specific to the polynucleotides of the present invention, so that transcript levels corresponding to the polynucleotides of the present invention may be

25 quantified. The transcript levels in the treated biological sample are compared with levels in an untreated biological sample. Differences in the transcript levels between the two samples are indicative of a toxic response caused by the test compound in the treated sample.

Another particular embodiment relates to the use of the polypeptide sequences of the present invention to analyze the proteome of a tissue or cell type. The term proteome refers to the global

30 pattern of protein expression in a particular tissue or cell type. Each protein component of a proteome can be subjected individually to further analysis. Proteome expression patterns, or profiles, are analyzed by quantifying the number of expressed proteins and their relative abundance under given conditions and at a given time. A profile of a cell's proteome may thus be generated by separating and analyzing the polypeptides of a particular tissue or cell type. In one embodiment, the separation is

achieved using two-dimensional gel electrophoresis, in which proteins from a sample are separated by isoelectric focusing in the first dimension, and then according to molecular weight by sodium dodecyl sulfate slab gel electrophoresis in the second dimension (Steiner and Anderson, *supra*). The proteins are visualized in the gel as discrete and uniquely positioned spots, typically by staining the gel with an agent such as Coomassie Blue or silver or fluorescent stains. The optical density of each protein spot is generally proportional to the level of the protein in the sample. The optical densities of equivalently positioned protein spots from different samples, for example, from biological samples either treated or untreated with a test compound or therapeutic agent, are compared to identify any changes in protein spot density related to the treatment. The proteins in the spots are partially sequenced using, for example, standard methods employing chemical or enzymatic cleavage followed by mass spectrometry. The identity of the protein in a spot may be determined by comparing its partial sequence, preferably of at least 5 contiguous amino acid residues, to the polypeptide sequences of the present invention. In some cases, further sequence data may be obtained for definitive protein identification.

A proteomic profile may also be generated using antibodies specific for PKIN to quantify the levels of PKIN expression. In one embodiment, the antibodies are used as elements on a microarray, and protein expression levels are quantified by exposing the microarray to the sample and detecting the levels of protein bound to each array element (Lueking, A. et al. (1999) *Anal. Biochem.* 270:103-111; Mendoz, L.G. et al. (1999) *Biotechniques* 27:778-788). Detection may be performed by a variety of methods known in the art, for example, by reacting the proteins in the sample with a thiol- or amino-reactive fluorescent compound and detecting the amount of fluorescence bound at each array element.

Toxicant signatures at the proteome level are also useful for toxicological screening, and should be analyzed in parallel with toxicant signatures at the transcript level. There is a poor correlation between transcript and protein abundances for some proteins in some tissues (Anderson, N.L. and J. Seilhamer (1997) *Electrophoresis* 18:533-537), so proteome toxicant signatures may be useful in the analysis of compounds which do not significantly affect the transcript image, but which alter the proteomic profile. In addition, the analysis of transcripts in body fluids is difficult, due to rapid degradation of mRNA, so proteomic profiling may be more reliable and informative in such cases.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins that are expressed in the treated biological sample are separated so that the amount of each protein can be quantified. The amount of each protein is compared to the amount of the corresponding protein in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the

test compound in the treated sample. Individual proteins are identified by sequencing the amino acid residues of the individual proteins and comparing these partial sequences to the polypeptides of the present invention.

In another embodiment, the toxicity of a test compound is assessed by treating a biological sample containing proteins with the test compound. Proteins from the biological sample are incubated with antibodies specific to the polypeptides of the present invention. The amount of protein recognized by the antibodies is quantified. The amount of protein in the treated biological sample is compared with the amount in an untreated biological sample. A difference in the amount of protein between the two samples is indicative of a toxic response to the test compound in the treated sample.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.) Various types of microarrays are well known and thoroughly described in DNA Microarrays: A Practical Approach, M. Schena, ed. (1999) Oxford University Press, London, hereby expressly incorporated by reference.

In another embodiment of the invention, nucleic acid sequences encoding PKIN may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. Either coding or noncoding sequences may be used, and in some instances, noncoding sequences may be preferable over coding sequences. For example, conservation of a coding sequence among members of a multi-gene family may potentially cause undesired cross hybridization during chromosomal mapping. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price, C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.) Once mapped, the nucleic acid sequences of the invention may be used to develop genetic linkage maps, for example, which correlate the inheritance of a disease state with the inheritance of a particular chromosome region or restriction fragment length polymorphism (RFLP). (See, for example, Lander, E.S. and D. Botstein (1986) Proc. Natl. Acad. Sci. USA 83:7353-7357.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding PKIN on a

physical map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder and thus may further positional cloning efforts.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps.

- 5 Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the exact chromosomal locus is not known. This information is valuable to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the gene or genes responsible for a disease or syndrome have been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any
10 sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the instant invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

- In another embodiment of the invention, PKIN, its catalytic or immunogenic fragments, or
15 oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between PKIN and the agent being tested may be measured.

- Another technique for drug screening provides for high throughput screening of compounds
20 having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with PKIN, or fragments thereof, and washed. Bound PKIN is then detected by methods well known in the art. Purified PKIN can also be coated directly onto plates for use in the aforementioned drug screening techniques. :
25 Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

- In another embodiment, one may use competitive drug screening assays in which neutralizing antibodies capable of binding PKIN specifically compete with a test compound for binding PKIN. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more
30 antigenic determinants with PKIN.

In additional embodiments, the nucleotide sequences which encode PKIN may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

5 The disclosures of all patents, applications and publications, mentioned above and below and including U.S. Ser. No. 60/229,873, U.S. Ser. No. 60/231,357, U.S. Ser. No. 60/232,654, U.S. Ser. No. 60/234,902, U.S. Ser. No. 60/236,499, U.S. Ser. No. 60/238,389, and U.S. Ser. No. 60/240,542, are expressly incorporated by reference herein.

10

EXAMPLES

I. Construction of cDNA Libraries

Incyte cDNAs were derived from cDNA libraries described in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA) and shown in Table 4, column 5. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in
15 phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA
20 purity. In some cases, RNA was treated with DNase. For most libraries, poly(A)+ RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

25 In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP vector system (Stratagene) or SUPERScript plasmid system (Life Technologies), using

PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), PCDNA2.1 plasmid (Invitrogen, Carlsbad CA), PBK-CMV plasmid (Stratagene), PCR2-TOPOTA (Invitrogen), PCMV-ICIS (Stratagene), or pINCY (Incyte Genomics, Palo Alto CA), or derivatives thereof. Recombinant plasmids were transformed into competent *E. coli* cells including XL1-Blue, XL1-BlueMRF, or SOLR
5 from Stratagene or DH5 α , DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids obtained as described in Example I were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an
10 AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a
15 high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

20 III. Sequencing and Analysis

Incyte cDNA recovered in plasmids as described in Example II were sequenced as follows. Sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Applied Biosystems) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the
25 MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the
30 ABI PRISM 373 or 377 sequencing system (Applied Biosystems) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example VIII.

The polynucleotide sequences derived from Incyte cDNAs were validated by removing vector, linker, and poly(A) sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programming, and dinucleotide nearest neighbor analysis. The Incyte cDNA sequences or translations thereof were then queried against a selection of public

5 databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and hidden Markov model (HMM)-based protein family databases such as PFAM. (HMM is a probabilistic approach which analyzes consensus primary structures of gene families. See, for example, Eddy, S.R. (1996) *Curr. Opin. Struct. Biol.* 6:361-365.) The queries were performed using programs based on BLAST, FASTA, BLIMPS, and HMMER.

10 The Incyte cDNA sequences were assembled to produce full length polynucleotide sequences. Alternatively, GenBank cDNAs, GenBank ESTs, stitched sequences, stretched sequences, or Genscan-predicted coding sequences (see Examples IV and V) were used to extend Incyte cDNA assemblages to full length. Assembly was performed using programs based on Phred, Phrap, and Consed, and cDNA assemblages were screened for open reading frames using programs based on

15 GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length polypeptide sequences. Alternatively, a polypeptide of the invention may begin at any of the methionine residues of the full length translated polypeptide. Full length polypeptide sequences were subsequently analyzed by querying against databases such as the GenBank protein databases (genpept), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and hidden

20 Markov model (HMM)-based protein family databases such as PFAM. Full length polynucleotide sequences are also analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments are generated using default parameters specified by the CLUSTAL algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also

25 calculates the percent identity between aligned sequences.

Table 7 summarizes the tools, programs, and algorithms used for the analysis and assembly of Incyte cDNA and full length sequences and provides applicable descriptions, references, and threshold parameters. The first column of Table 7 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of

30 which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score or the lower the probability value, the greater the identity between two sequences).

The programs described above for the assembly and analysis of full length polynucleotide and polypeptide sequences were also used to identify polynucleotide sequence fragments from SEQ ID NO:25-48. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies are described in Table 4, column 4.

5 IV. Identification and Editing of Coding Sequences from Genomic DNA

Putative human kinases were initially identified by running the Genscan gene identification program against public genomic sequence databases (e.g., gbpri and gbhtg). Genscan is a general-purpose gene identification program which analyzes genomic DNA sequences from a variety of organisms (See Burge, C. and S. Karlin (1997) J. Mol. Biol. 268:78-94, and Burge, C. and S. Karlin
10 (1998) Curr. Opin. Struct. Biol. 8:346-354). The program concatenates predicted exons to form an assembled cDNA sequence extending from a methionine to a stop codon. The output of Genscan is a FASTA database of polynucleotide and polypeptide sequences. The maximum range of sequence for Genscan to analyze at once was set to 30 kb. To determine which of these Genscan predicted cDNA sequences encode human kinases, the encoded polypeptides were analyzed by querying against
15 PFAM models for human kinases. Potential human kinases were also identified by homology to Incyte cDNA sequences that had been annotated as human kinases. These selected Genscan-predicted sequences were then compared by BLAST analysis to the genpept and gbpri public databases. Where necessary, the Genscan-predicted sequences were then edited by comparison to the top BLAST hit from genpept to correct errors in the sequence predicted by Genscan, such as
20 extra or omitted exons. BLAST analysis was also used to find any Incyte cDNA or public cDNA coverage of the Genscan-predicted sequences, thus providing evidence for transcription. When Incyte cDNA coverage was available, this information was used to correct or confirm the Genscan predicted sequence. Full length polynucleotide sequences were obtained by assembling Genscan-predicted coding sequences with Incyte cDNA sequences and/or public cDNA sequences using the assembly
25 process described in Example III. Alternatively, full length polynucleotide sequences were derived entirely from edited or unedited Genscan-predicted coding sequences.

V. Assembly of Genomic Sequence Data with cDNA Sequence Data

"Stitched" Sequences

Partial cDNA sequences were extended with exons predicted by the Genscan gene
30 identification program described in Example IV. Partial cDNAs assembled as described in Example III were mapped to genomic DNA and parsed into clusters containing related cDNAs and Genscan exon predictions from one or more genomic sequences. Each cluster was analyzed using an algorithm based on graph theory and dynamic programming to integrate cDNA and genomic information, generating possible splice variants that were subsequently confirmed, edited, or extended to create a

full length sequence. Sequence intervals in which the entire length of the interval was present on more than one sequence in the cluster were identified, and intervals thus identified were considered to be equivalent by transitivity. For example, if an interval was present on a cDNA and two genomic sequences, then all three intervals were considered to be equivalent. This process allows unrelated but consecutive genomic sequences to be brought together, bridged by cDNA sequence. Intervals thus identified were then "stitched" together by the stitching algorithm in the order that they appear along their parent sequences to generate the longest possible sequence, as well as sequence variants. Linkages between intervals which proceed along one type of parent sequence (cDNA to cDNA or genomic sequence to genomic sequence) were given preference over linkages which change parent type (cDNA to genomic sequence). The resultant stitched sequences were translated and compared by BLAST analysis to the genpept and gbprl public databases. Incorrect exons predicted by Genscan were corrected by comparison to the top BLAST hit from genpept. Sequences were further extended with additional cDNA sequences, or by inspection of genomic DNA, when necessary.

"Stretched" Sequences

Partial DNA sequences were extended to full length with an algorithm based on BLAST analysis. First, partial cDNAs assembled as described in Example III were queried against public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases using the BLAST program. The nearest GenBank protein homolog was then compared by BLAST analysis to either Incyte cDNA sequences or GenScan exon predicted sequences described in Example IV. A chimeric protein was generated by using the resultant high-scoring segment pairs (HSPs) to map the translated sequences onto the GenBank protein homolog. Insertions or deletions may occur in the chimeric protein with respect to the original GenBank protein homolog. The GenBank protein homolog, the chimeric protein, or both were used as probes to search for homologous genomic sequences from the public human genome databases. Partial DNA sequences were therefore "stretched" or extended by the addition of homologous genomic sequences. The resultant stretched sequences were examined to determine whether it contained a complete gene.

VI. Chromosomal Mapping of PKIN Encoding Polynucleotides

The sequences which were used to assemble SEQ ID NO:25-48 were compared with sequences from the Incyte LIFESEQ database and public domain databases using BLAST and other implementations of the Smith-Waterman algorithm. Sequences from these databases that matched SEQ ID NO:25-48 were assembled into clusters of contiguous and overlapping sequences using assembly algorithms such as Phrap (Table 7). Radiation hybrid and genetic mapping data available from public resources such as the Stanford Human Genome Center (SHGC), Whitehead Institute for Genome Research (WIGR), and Génethon were used to determine if any of the clustered sequences

had been previously mapped. Inclusion of a mapped sequence in a cluster resulted in the assignment of all sequences of that cluster, including its particular SEQ ID NO., to that map location.

Map locations are represented by ranges, or intervals, of human chromosomes. The map position of an interval, in centiMorgans, is measured relative to the terminus of the chromosome's p-arm. (The centiMorgan (cM) is a unit of measurement based on recombination frequencies between chromosomal markers. On average, 1 cM is roughly equivalent to 1 megabase (Mb) of DNA in humans, although this can vary widely due to hot and cold spots of recombination.) The cM distances are based on genetic markers mapped by Généthon which provide boundaries for radiation hybrid markers whose sequences were included in each of the clusters. Human genome maps and other resources available to the public, such as the NCBI "GeneMap'99" World Wide Web site (<http://www.ncbi.nlm.nih.gov/genemap/>), can be employed to determine if previously identified disease genes map within or in proximity to the intervals indicated above.

VII. Analysis of Polynucleotide Expression

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, *supra*, ch. 7; Ausubel (1995) *supra*, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in cDNA databases such as GenBank or LIFESEQ (Incyte Genomics). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\text{BLAST Score} \times \text{Percent Identity}}{5 \times \text{minimum \{length(Seq. 1), length(Seq. 2)\}}}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. The product score is a normalized value between 0 and 100, and is calculated as follows: the BLAST score is multiplied by the percent nucleotide identity and the product is divided by (5 times the length of the shorter of the two sequences). The BLAST score is calculated by assigning a score of +5 for every base that matches in a high-scoring segment pair (HSP), and -4 for every mismatch. Two sequences may share more than one HSP (separated by gaps). If there is more than one HSP, then the pair with the highest BLAST score is used to calculate the product score. The product score represents a balance between fractional overlap and quality in a

BLAST alignment. For example, a product score of 100 is produced only for 100% identity over the entire length of the shorter of the two sequences being compared. A product score of 70 is produced either by 100% identity and 70% overlap at one end, or by 88% identity and 100% overlap at the other. A product score of 50 is produced either by 100% identity and 50% overlap at one end, or 79% identity and 100% overlap.

Alternatively, polynucleotide sequences encoding PKIN are analyzed with respect to the tissue sources from which they were derived. For example, some full length sequences are assembled, at least in part, with overlapping Incyte cDNA sequences (see Example III). Each cDNA sequence is derived from a cDNA library constructed from a human tissue. Each human tissue is classified into one of the following organ/tissue categories: cardiovascular system; connective tissue; digestive system; embryonic structures; endocrine system; exocrine glands; genitalia, female; genitalia, male; germ cells; hemic and immune system; liver; musculoskeletal system; nervous system; pancreas; respiratory system; sense organs; skin; stomatognathic system; unclassified/mixed; or urinary tract. The number of libraries in each category is counted and divided by the total number of libraries across all categories. Similarly, each human tissue is classified into one of the following disease/condition categories: cancer, cell line, developmental, inflammation, neurological, trauma, cardiovascular, pooled, and other, and the number of libraries in each category is counted and divided by the total number of libraries across all categories. The resulting percentages reflect the tissue- and disease-specific expression of cDNA encoding PKIN. cDNA sequences and cDNA library/tissue information are found in the LIFESEQ GOLD database (Incyte Genomics, Palo Alto CA).

VIII. Extension of PKIN Encoding Polynucleotides

Full length polynucleotide sequences were also produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer was synthesized to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2+} , $(NH_4)_2SO_4$,

and 2-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 µl to 10 µl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent *E. coli* cells. Transformed cells were selected on antibiotic-containing media, and individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min; Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethylsulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Applied Biosystems).

In like manner, full length polynucleotide sequences are verified using the above procedure or are used to obtain 5' regulatory sequences using the above procedure along with oligonucleotides designed for such extension, and an appropriate genomic library.

IX. Labeling and Use of Individual Hybridization Probes

5 Hybridization probes derived from SEQ ID NO:25-48 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μ Ci of
10 [γ -³²P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10⁷ counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase
15 I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate.
20 Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

X. Microarrays

The linkage or synthesis of array elements upon a microarray can be achieved utilizing photolithography, piezoelectric printing (ink-jet printing, See, e.g., Baldeschweiler, *supra*), mechanical
25 microspotting technologies, and derivatives thereof. The substrate in each of the aforementioned technologies should be uniform and solid with a non-porous surface (Skena (1999), *supra*). Suggested substrates include silicon, silica, glass slides, glass chips, and silicon wafers. Alternatively, a procedure analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may
30 be produced using available methods and machines well known to those of ordinary skill in the art and may contain any appropriate number of elements. (See, e.g., Skena, M. et al. (1995) *Science* 270:467-470; Shalon, D. et al. (1996) *Genome Res.* 6:639-645; Marshall, A. and J. Hodgson (1998) *Nat. Biotechnol.* 16:27-31.)

Full length cDNAs, Expressed Sequence Tags (ESTs), or fragments or oligomers thereof may comprise the elements of the microarray. Fragments or oligomers suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). The array elements are hybridized with polynucleotides in a biological sample. The polynucleotides in the biological sample are conjugated to a fluorescent label or other molecular tag for ease of detection. After hybridization, nonhybridized nucleotides from the biological sample are removed, and a fluorescence scanner is used to detect hybridization at each array element. Alternatively, laser desorption and mass spectrometry may be used for detection of hybridization. The degree of complementarity and the relative abundance of each polynucleotide which hybridizes to an element on the microarray may be assessed. In one embodiment, microarray preparation and usage is described in detail below.

Tissue or Cell Sample Preparation

Total RNA is isolated from tissue samples using the guanidinium thiocyanate method and poly(A)⁺ RNA is purified using the oligo-(dT) cellulose method. Each poly(A)⁺ RNA sample is reverse transcribed using MMLV reverse-transcriptase, 0.05 pg/ μ l oligo-(dT) primer (21mer), 1X first strand buffer, 0.03 units/ μ l RNase inhibitor, 500 μ M dATP, 500 μ M dGTP, 500 μ M dTTP, 40 μ M dCTP, 40 μ M dCTP-Cy3 (BDS) or dCTP-Cy5 (Amersham Pharmacia Biotech). The reverse transcription reaction is performed in a 25 ml volume containing 200 ng poly(A)⁺ RNA with GEMBRIGHT kits (Incyte). Specific control poly(A)⁺ RNAs are synthesized by *in vitro* transcription from non-coding yeast genomic DNA. After incubation at 37°C for 2 hr, each reaction sample (one with Cy3 and another with Cy5 labeling) is treated with 2.5 ml of 0.5M sodium hydroxide and incubated for 20 minutes at 85°C to stop the reaction and degrade the RNA. Samples are purified using two successive CHROMA SPIN 30 gel filtration spin columns (CLONTECH Laboratories, Inc. (CLONTECH), Palo Alto CA) and after combining, both reaction samples are ethanol precipitated using 1 ml of glycogen (1 mg/ml), 60 ml sodium acetate, and 300 ml of 100% ethanol. The sample is then dried to completion using a SpeedVAC (Savant Instruments Inc., Holbrook NY) and resuspended in 14 μ l 5X SSC/0.2% SDS.

Microarray Preparation

Sequences of the present invention are used to generate array elements. Each array element is amplified from bacterial cells containing vectors with cloned cDNA inserts. PCR amplification uses primers complementary to the vector sequences flanking the cDNA insert. Array elements are amplified in thirty cycles of PCR from an initial quantity of 1-2 ng to a final quantity greater than 5 μ g. Amplified array elements are then purified using SEPHACRYL-400 (Amersham Pharmacia Biotech).

Purified array elements are immobilized on polymer-coated glass slides. Glass microscope slides (Corning) are cleaned by ultrasound in 0.1% SDS and acetone, with extensive distilled water washes between and after treatments. Glass slides are etched in 4% hydrofluoric acid (VWR Scientific Products Corporation (VWR), West Chester PA), washed extensively in distilled water, and
5 coated with 0.05% aminopropyl silane (Sigma) in 95% ethanol. Coated slides are cured in a 110°C oven.

Array elements are applied to the coated glass substrate using a procedure described in US Patent No. 5,807,522, incorporated herein by reference. 1 μ l of the array element DNA, at an average concentration of 100 ng/ μ l, is loaded into the open capillary printing element by a high-speed robotic
10 apparatus. The apparatus then deposits about 5 nl of array element sample per slide.

Microarrays are UV-crosslinked using a STRATALINKER UV-crosslinker (Stratagene). Microarrays are washed at room temperature once in 0.2% SDS and three times in distilled water. Non-specific binding sites are blocked by incubation of microarrays in 0.2% casein in phosphate buffered saline (PBS) (Tropix, Inc., Bedford MA) for 30 minutes at 60°C followed by washes in 0.2%
15 SDS and distilled water as before.

Hybridization

Hybridization reactions contain 9 μ l of sample mixture consisting of 0.2 μ g each of Cy3 and Cy5 labeled cDNA synthesis products in 5X SSC, 0.2% SDS hybridization buffer. The sample mixture is heated to 65°C for 5 minutes and is aliquoted onto the microarray surface and covered with
20 an 1.8 cm² coverslip. The arrays are transferred to a waterproof chamber having a cavity just slightly larger than a microscope slide. The chamber is kept at 100% humidity internally by the addition of 140 μ l of 5X SSC in a corner of the chamber. The chamber containing the arrays is incubated for about 6.5 hours at 60°C. The arrays are washed for 10 min at 45°C in a first wash buffer (1X SSC, 0.1% SDS), three times for 10 minutes each at 45°C in a second wash buffer (0.1X SSC), and dried.

Detection

Reporter-labeled hybridization complexes are detected with a microscope equipped with an Innova 70 mixed gas 10 W laser (Coherent, Inc., Santa Clara CA) capable of generating spectral lines at 488 nm for excitation of Cy3 and at 632 nm for excitation of Cy5. The excitation laser light is focused on the array using a 20X microscope objective (Nikon, Inc., Melville NY). The slide
30 containing the array is placed on a computer-controlled X-Y stage on the microscope and raster-scanned past the objective. The 1.8 cm x 1.8 cm array used in the present example is scanned with a resolution of 20 micrometers.

In two separate scans, a mixed gas multiline laser excites the two fluorophores sequentially. Emitted light is split, based on wavelength, into two photomultiplier tube detectors (PMT R1477,

Hamamatsu Photonics Systems, Bridgewater NJ) corresponding to the two fluorophores. Appropriate filters positioned between the array and the photomultiplier tubes are used to filter the signals. The emission maxima of the fluorophores used are 565 nm for Cy3 and 650 nm for Cy5. Each array is typically scanned twice, one scan per fluorophore using the appropriate filters at the laser source, although the apparatus is capable of recording the spectra from both fluorophores simultaneously.

The sensitivity of the scans is typically calibrated using the signal intensity generated by a cDNA control species added to the sample mixture at a known concentration. A specific location on the array contains a complementary DNA sequence, allowing the intensity of the signal at that location to be correlated with a weight ratio of hybridizing species of 1:100,000. When two samples from different sources (e.g., representing test and control cells), each labeled with a different fluorophore, are hybridized to a single array for the purpose of identifying genes that are differentially expressed, the calibration is done by labeling samples of the calibrating cDNA with the two fluorophores and adding identical amounts of each to the hybridization mixture.

The output of the photomultiplier tube is digitized using a 12-bit RTI-835H analog-to-digital (A/D) conversion board (Analog Devices, Inc., Norwood MA) installed in an IBM-compatible PC computer. The digitized data are displayed as an image where the signal intensity is mapped using a linear 20-color transformation to a pseudocolor scale ranging from blue (low signal) to red (high signal). The data is also analyzed quantitatively. Where two different fluorophores are excited and measured simultaneously, the data are first corrected for optical crosstalk (due to overlapping emission spectra) between the fluorophores using each fluorophore's emission spectrum.

A grid is superimposed over the fluorescence signal image such that the signal from each spot is centered in each element of the grid. The fluorescence signal within each element is then integrated to obtain a numerical value corresponding to the average intensity of the signal. The software used for signal analysis is the GEMTOOLS gene expression analysis program (Incyte).

XI. Complementary Polynucleotides

Sequences complementary to the PKIN-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring PKIN. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of PKIN. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the PKIN-encoding transcript.

XII. Expression of PKIN

Expression and purification of PKIN is achieved using bacterial or virus-based expression systems. For expression of PKIN in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac (tac)* hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express PKIN upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of PKIN in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding PKIN by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, PKIN is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from PKIN at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified PKIN obtained by these methods can be used directly in the assays shown in Examples XVI, XVII, XVIII, and XIX where applicable.

XIII. Functional Assays

PKIN function is assessed by expressing the sequences encoding PKIN at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include PCMV SPORT (Life Technologies) and PCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μ g of recombinant vector are transiently transfected into

a human cell line, for example, an endothelial or hematopoietic cell line, using either liposome formulations or electroporation. 1-2 μ g of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of PKIN on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding PKIN and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding PKIN and other genes of interest can be analyzed by northern analysis or microarray techniques.

XIV. Production of PKIN Specific Antibodies

PKIN substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) *Methods Enzymol.* 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the PKIN amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Applied Biosystems) using Fmoc chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase immunogenicity. (See, e.g., Ausubel, 1995, *supra*.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-PKIN activity by, for example, binding the peptide or PKIN to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XV. Purification of Naturally Occurring PKIN Using Specific Antibodies

Naturally occurring or recombinant PKIN is substantially purified by immunoaffinity chromatography using antibodies specific for PKIN. An immunoaffinity column is constructed by covalently coupling anti-PKIN antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing PKIN are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of PKIN (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/PKIN binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and PKIN is collected.

XVI. Identification of Molecules Which Interact with PKIN

PKIN, or biologically active fragments thereof, are labeled with ¹²⁵I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) *Biochem. J.* 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled PKIN, washed, and any wells with labeled PKIN complex are assayed. Data obtained using different concentrations of PKIN are used to calculate values for the number, affinity, and association of PKIN with the candidate molecules.

Alternatively, molecules interacting with PKIN are analyzed using the yeast two-hybrid system as described in Fields, S. and O. Song (1989) *Nature* 340:245-246, or using commercially available kits based on the two-hybrid system, such as the MATCHMAKER system (Clontech).

PKIN may also be used in the PATHCALLING process (CuraGen Corp., New Haven CT) which employs the yeast two-hybrid system in a high-throughput manner to determine all interactions between the proteins encoded by two large libraries of genes (Nandabalan, K. et al. (2000) U.S. Patent No. 6,057,101).

XVII. Demonstration of PKIN Activity

Generally, protein kinase activity is measured by quantifying the phosphorylation of a protein substrate by PKIN in the presence of [γ - ^{32}P]ATP. PKIN is incubated with the protein substrate, ^{32}P -ATP, and an appropriate kinase buffer. The ^{32}P incorporated into the substrate is separated from free ^{32}P -ATP by electrophoresis and the incorporated ^{32}P is counted using a radioisotope counter.

- 5 The amount of incorporated ^{32}P is proportional to the activity of PKIN. A determination of the specific amino acid residue phosphorylated is made by phosphoamino acid analysis of the hydrolyzed protein.

In one alternative, protein kinase activity is measured by quantifying the transfer of gamma phosphate from adenosine triphosphate (ATP) to a serine, threonine or tyrosine residue in a protein
10 substrate. The reaction occurs between a protein kinase sample with a biotinylated peptide substrate and gamma ^{32}P -ATP. Following the reaction, free avidin in solution is added for binding to the biotinylated ^{32}P -peptide product. The binding sample then undergoes a centrifugal ultrafiltration process with a membrane which will retain the product-avidin complex and allow passage of free gamma ^{32}P -ATP. The reservoir of the centrifuged unit containing the ^{32}P -peptide product as retentate
15 is then counted in a scintillation counter. This procedure allows assay of any type of protein kinase sample, depending on the peptide substrate and kinase reaction buffer selected. This assay is provided in kit form (ASUA, Affinity Ultrafiltration Separation Assay, Transbio Corporation, Baltimore MD, U.S. Patent No. 5,869,275). Suggested substrates and their respective enzymes include but are not limited to: Histone H1 (Sigma) and p34^{cdc2}kinase, Annexin I, Angiotensin (Sigma) and EGF receptor
20 kinase, Annexin II and *src* kinase, ERK1 & ERK2 substrates and MEK, and myelin basic protein and ERK (Pearson, J.D. et al. (1991) Methods Enzymol. 200:62-81).

In another alternative, protein kinase activity of PKIN is demonstrated in an assay containing PKIN, 50 μl of kinase buffer, 1 μg substrate, such as myelin basic protein (MBP) or synthetic peptide substrates, 1 mM DTT, 10 μg ATP, and 0.5 μCi [γ - ^{32}P]ATP. The reaction is incubated at 30°C for
25 30 minutes and stopped by pipetting onto P81 paper. The unincorporated [γ - ^{32}P]ATP is removed by washing and the incorporated radioactivity is measured using a scintillation counter. Alternatively, the reaction is stopped by heating to 100°C in the presence of SDS loading buffer and resolved on a 12% SDS polyacrylamide gel followed by autoradiography. The amount of incorporated ^{32}P is proportional to the activity of PKIN.

30 In yet another alternative, adenylate kinase or guanylate kinase activity may be measured by the incorporation of ^{32}P from [γ - ^{32}P]ATP into ADP or GDP using a gamma radioisotope counter. The enzyme, in a kinase buffer, is incubated together with the appropriate nucleotide mono-phosphate substrate (AMP or GMP) and ^{32}P -labeled ATP as the phosphate donor. The reaction is incubated at 37°C and terminated by addition of trichloroacetic acid. The acid extract is neutralized and subjected

to gel electrophoresis to separate the mono-, di-, and triphosphonucleotide fractions. The diphosphonucleotide fraction is excised and counted. The radioactivity recovered is proportional to the enzyme activity.

In yet another alternative, other assays for PKIN include scintillation proximity assays (SPA),
5 scintillation plate technology and filter binding assays. Useful substrates include recombinant proteins tagged with glutathione transferase, or synthetic peptide substrates tagged with biotin. Inhibitors of PKIN activity, such as small organic molecules, proteins or peptides, may be identified by such assays.

XVIII. Enhancement/Inhibition of Protein Kinase Activity

Agonists or antagonists of PKIN activation or inhibition may be tested using assays described
10 in section XVII. Agonists cause an increase in PKIN activity and antagonists cause a decrease in PKIN activity.

XIX. Kinase Binding Assay

Binding of PKIN to a FLAG-CD44 cyt fusion protein can be determined by incubating PKIN
to anti-PKIN-conjugated immunoaffinity beads followed by incubating portions of the beads (having
15 10-20 ng of protein) with 0.5 ml of a binding buffer (20 mM Tris-HCL (pH 7.4), 150 mM NaCl, 0.1% bovine serum albumin, and 0.05% Triton X-100) in the presence of ¹²⁵I-labeled FLAG-CD44cyt fusion protein (5,000 cpm/ng protein) at 4 °C for 5 hours. Following binding, beads were washed thoroughly in the binding buffer and the bead-bound radioactivity measured in a scintillation counter (Bourguignon, L.Y.W. et al. (2001) J. Biol. Chem. 276:7327-7336). The amount of incorporated ³²P is proportional
20 to the amount of bound PKIN.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be
25 understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

Table 1

| Incyte Project ID | Polypeptide SEQ ID NO: | Incyte Polypeptide ID | Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID |
|----------------------|---------------------------|--------------------------|------------------------------|-----------------------------|
| 7312543 | 1 | 7312543CD1 | 25 | 7312543CB1 |
| 7477427 | 2 | 7477427CD1 | 26 | 7477427CB1 |
| 7481495 | 3 | 7481495CD1 | 27 | 7481495CB1 |
| 55053189 | 4 | 55053189CD1 | 28 | 55053189CB1 |
| 7474797 | 5 | 7474797CD1 | 29 | 7474797CB1 |
| 3296272 | 6 | 3296272CD1 | 30 | 3296272CB1 |
| 1989319 | 7 | 1989319CD1 | 31 | 1989319CB1 |
| 079284 | 8 | 079284CD1 | 32 | 079284CB1 |
| 5502218 | 9 | 5502218CD1 | 33 | 5502218CB1 |
| 55056054 | 10 | 55056054CD1 | 34 | 55056054CB1 |
| 7481989 | 11 | 7481989CD1 | 35 | 7481989CB1 |
| 55052990 | 12 | 55052990CD1 | 36 | 55052990CB1 |
| 7482377 | 13 | 7482377CD1 | 37 | 7482377CB1 |
| 7758364 | 14 | 7758364CD1 | 38 | 7758364CB1 |
| 5850001 | 15 | 5850001CD1 | 39 | 5850001CB1 |
| 7477062 | 16 | 7477062CD1 | 40 | 7477062CB1 |
| 7477207 | 17 | 7477207CD1 | 41 | 7477207CB1 |
| 4022651 | 18 | 4022651CD1 | 42 | 4022651CB1 |
| 7274927 | 19 | 7274927CD1 | 43 | 7274927CB1 |
| 7946584 | 20 | 7946584CD1 | 44 | 7946584CB1 |
| 8088078 | 21 | 8088078CD1 | 45 | 8088078CB1 |
| 2674269 | 22 | 2674269CD1 | 46 | 2674269CB1 |
| 7472409 | 23 | 7472409CD1 | 47 | 7472409CB1 |
| 7477484 | 24 | 7477484CD1 | 48 | 7477484CB1 |

Table 2

| Polypeptide SEQ ID NO: | Incyte Polypeptide ID | GenBank ID NO: | Probability score | GenBank Homolog |
|---------------------------|-----------------------------|-------------------|----------------------|--|
| 1 | 7312543CD1 | g4115429 | 9.00E-215 | [Rattus norvegicus] serin/threonine protein kinase (Amano, M. et al. (1996) Science 271:648-650) |
| 2 | 7477427CD1 | g2736151 | 0 | [Rattus norvegicus] myotonic dystrophy kinase-related (Leung, T. et al. (1998) Mol. Cell. Biol. 18 (1), 130- 140) |
| 3 | 7481495CD1 | g10945428 | 0 | [fl][Homo sapiens] membrane-associated guanylate kinase MAGI3 (Wu, Y. et al. (2000) J. Biol. Chem. 275 (28), 21477- 21485) |
| 4 | 55053189CD1 | g1360110 | 5.80E-73 | [Plasmodium falciparum] mitogen-activated protein kinase 1, serine/threonine protein kinase (Doerig, C.M. et al. (1996) Gene 177 (1-2), 1-6) |
| | | g4220888 | 5.30E-171 | [Rattus norvegicus] extracellular signal-regulated kinase 7; ERK7 (Abe, M.K. et al. (1999) Mol. Cell. Biol. 19 (2), 1301- 1312) |
| | | g2131000 | 4.20E-70 | [Leishmania mexicana] MAP-kinase homologue (Wiese, M. (1998) EMBO J. 17 (9), 2619-2628) |
| 5 | 7474797CD1 | g404634 | 2.60E-54 | [Mus musculus] serine/threonine kinase (Bielke, W. et al. (1994) Gene 139 (2), 235-239) |
| 6 | 3296272CD1 | g6690020 | 1.60E-157 | [Mus musculus] pantothenate kinase 1 beta (Rock, C.O. et al. (2000) J. Biol. Chem. 275 (2), 1377- 1383) |
| 7 | 1989319CD1 | g6760436 | 9.20E-125 | [Gallus gallus] gin-induced kinase (Xia, Y. et al. (2000) Biochem. Biophys. Res. Commun. 276 (2), 564-570) |
| 8 | 79284CD1 | g5757703 | 0 | [Mus musculus] syntrophin-associated serine-threonine protein kinase (Lumeng, C. et al. (1999) Nat. Neurosci. 2 (7), 611-617) |
| 9 | 5502218CD1 | g8272557 | 0 | [Rattus norvegicus] protein kinase WNK1 (Xu, B. et al. (2000) J. Biol. Chem. 275 (22), 16795- 16801) |

Table 2 (cont.)

| Polypeptide SEQ ID NO: | Incyte Polypeptide ID | GenBank ID NO: | Probability score | GenBank Homolog |
|---------------------------|-----------------------------|-----------------------|----------------------|---|
| 10 | 55056054CD1 | g162787 | 1.80E-213 | [Bos taurus] cAMP-dependent protein kinase II-beta catalytic (Wiemann, S. et al. (1991) J. Biol. Chem. 266, 5140-5145) |
| 11 | 7481989CD1 | g529073 | 8.20E-18 | [Mus musculus] tyrosine-specific protein kinase (Kohmura, N. et al. (1994) Mol. Cell. Biol. 14 (10), 6915-6925) |
| 12 | 55052990CD1 | g10177211 | 4.00E-21 | [fl1][Arabidopsis thaliana] protein kinase |
| 13 | 7482377CD1 | g12005724 g3851202 | 0 0 | [5' incm][Homo sapiens] mixed lineage kinase MLK1 [Homo sapiens] MAGUK family member ZO-3 (Haskins, J. et al. (1998) J. Cell Biol. 141:199-208) |
| 14 | 7758364CD1 | g6716518 | 4.40E-266 | [Mus musculus] doublecortin-like kinase (Burgess, H.A. et al. (1999) J. Neurosci. Res. 58 (4), 567-575) |
| 15 | 5850001CD1 | g6690020 | 9.90E-165 | [Mus musculus] pantothenate kinase 1 beta (Rock, C.O. et al. (2000) J. Biol. Chem. 275 (2), 1377-1383) |
| 16 | 7477062CD1 | g4115429 | 7.90E-53 | [Rattus norvegicus] serin/threonine protein kinase |
| 17 | 7477207CD1 | g12830335 | 1.00E-130 | [5' incm][Homo sapiens] ba55008.2 (novel protein kinase) |
| 18 | 4022651CD1 | g3136154 g3217028 | 1.10E-17 0 | [Mus musculus] UNC-51-like kinase ULK1 (Kuroyanagi, H., et al. (1998) Genomics 51:76-85) [Homo sapiens] putative serine/threonine protein kinase (Stanchi, F. et al. (2001) Yeast 18 (1), 69-80) |
| 19 | 7274927CD1 | g286232 | 3.10E-76 | [Rattus norvegicus] nucleoside diphosphate kinase beta isoform (Shimada, N. et al. (1993) J. Biol. Chem. 268 (4), 2583-2589) |
| 20 | 7946584CD1 | g7161864 | 7.30E-148 | [Mus musculus] serine/threonine protein kinase (Ruiz-Perez, V.L. et al. (2000) Nat. Genet. 24 (3), 283-286) |
| 21 | 8088078CD1 | g189992 | 1.20E-13 | [Homo sapiens] protein kinase C-gamma (Coussens, L. et al. (1986) Science 233 (4766), 859-866) |

Table 2 (cont.)

| Polypeptide SEQ ID NO: | Incyte Polypeptide ID | GenBank ID NO: | Probability score | GenBank Homolog |
|---------------------------|-----------------------------|-------------------|----------------------|--|
| 22 | 2674269CD1 | g256855 | 5.60E-59 | [Mus sp.] serine/threonine- and tyrosine-specific protein kinase, Nekl=NIMA cell cycle regulator homolog (Letwin, K. et al. (1992) EMBO J. 11 (10), 3521-3531) |
| 23 | 7472409CD1 | g256855 | 8.00E-64 | [Mus sp.] serine/threonine- and tyrosine-specific protein kinase, Nekl=NIMA cell cycle regulator homolog (Letwin, K. et al. (1992) EMBO J. 11 (10), 3521-3531) |
| 24 | 7477484CD1 | g2459993 | 1.50E-153 | [Mus musculus] apoptosis associated tyrosine kinase (Gaozza, E. et al. (1997) Oncogene 15:3127-35) |

Table 3

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|-------------------------------|--|---|
| 1 | 7312543CD1 | 424 | S209 S257 S326 T150 T198 T215 T232 T285 T40 T418 | N85 | Eukaryotic protein kinase domain pkinase: Y53-V309 PROTEIN KINASE DOMAIN DM00004 JCI446 20-261: E54-R303 DM00004 P27448 58-297: L55-G304 DM00004 I48609 55-294: L55-G304 DM00004 Q05512 55-294: L55-G304 Tyrosine kinase catalytic site PR00109: Q128-P141, F164-L182, V234-A256 Protein kinase Ser/Thr active site domain Protein_Kinase_St: L170-L182 Protein kinase signatures and profile protein_kinase_tyr.prf: T150-G202 transmembrane domain: L228-T248 | HMME PFAM BLAST_DOMO BLIMPS_PRINTS MOTIFS PROFILES SCAN HMME |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|---|--|---|
| 2 | 7477427CD1 | 1719 | S167 S286 S344 S364 S369 S411 S459 S475 S507 S555 S616 S705 S750 S752 S781 S813 S877 S884 S917 S926 S940 S1532 T30 T423 T591 T624 T64 T691 T746 T780 T788 T959 T981 T999 Y358 S1142 T1172 T1242 S1283 S1406 S1607 S1651 S1271 S1306 T1492 S1517 S1532 S1622 S1643 S1680 S1700 T1712 Y1201 T1070 | N560 N792 N854 N1629 N1688 N1691 | Eukaryotic protein kinase domain pkinese: F77-F343 Protein kinase C terminal domain pkinese_C: S344-D372 PROTEIN KINASE DOMAIN DM00004 Q09013 83-336: I79-Q331 DM00004 S42867 75-498: I79-L226, V238-Y404, P1602-D1677 DM00004 I38133 90-369: E78-L226, V238-G330 DM00004 P53894 353-658: L80-G221, D205-Q331 Tyrosine kinase catalytic site PR00109: M154-S167, S191-M209, C263-E285 MYTONIC DYSTROPHY KINASE RELATED CDC42BINDING KINASE PHORBOLESTER BINDING PD143271: R1592-P1719 PD011252: D833-P994 PD075023: E630-N713 PD150840: W1467-S1591 Phorbol ester/diacylglycerol binding domain DAG_PE-bind: H1000-C1049 Pleckstrin homology domain PH: T1070-K1188 Domain found in NIK1-like kinase, mouse citron CNH: K1215-K1499 Leucine_Zipper: L772-L793, L779-L800, L786-L807 | HMMER_PFAM HMMER_PFAM BLAST_DOMO BLIMPS_PRINTS BLAST_PRODOM HMMER_PFAM HMMER_PFAM HMMER_PFAM MOTIFS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|--------------------------------|--|--|
| 2 | | | | | Protein kinase ATP binding domain Protein_Kinase_Atp: I83-K106 Protein kinase Ser/Thr active site domain Protein_Kinase_St: Y197-M209 Phorbol esters/DAG binding domain dag_pe_binding_domain.prf: C1013-A1071 | MOTIFS MOTIFS PROFILESCAN |
| 3 | 7481495CD1 | 1125 | S218 S227 S235 S278 S387 S388 S412 S572 S61 S66 S699 S785 S832 S889 S910 S949 S974 S987 S991 S1034 T102 T146 T190 T223 T224 T320 T365 T4 T417 T469 T520 T663 T668 T713 T805 T83 T868 Y303 Y353 | N249 N274 N277 N487 N629 | Guanylate kinase: T147-E243 Guanylate kinase protein BL00856: I143-I163 PROTEIN GUANYLATE KINASE MEMBRANE ASSOCIATED ATROPHIN1 INTERACTING INVERTED PUTATIVE BAIL ASSOCIATED PD021703: M1-T146 PROTEIN GUANYLATE KINASE MEMBRANE ASSOCIATED ATROPHIN1 INTERACTING INVERTED PAC PD029527: L326-Q379, E575-T663 Guanylate_Kinase: T146-I163 WW proline-rich motif binding domain WW: L295-P324, L341-P370 WW/rsp5/WWP domain BL01159: Y310-P324 WW domain signature PR00403: L295-M308, Y310-P324 Ww_Domain_1: W299-P324, W345-P370 PDZ domain found in signaling proteins PDZ: R410-G493, L576-G655, D724-K809, D851-E937, P1021-G1102 | HMMER_PPFAM BLIMPS_BLOCKS BLAST_PRODOR BLAST_PRODOR MOTIFS HMMER_PPFAM BLIMPS_BLOCKS BLIMPS_PRINTS MOTIFS HMMER_PPFAM |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|--|---|
| 3 | | | | | PDZ domain PF00595: I1062-N1072 ATP/GTP binding site (P-loop) Atp_Gtp_A: G778-S785 | BLIMPS_PFAM MOTIFS |
| 4 | 55053189CD1 | 500 | S161 S192 S238 S294 S359 S403 S75 T150 T273 T3 T308 T57 Y89 | N148 | KINASE PROTEIN TRANSFERASE ATP BINDING SERINE/THREONINE PROTEIN PHOSPHORYLATION RECEPTOR TYROSINE PROTEIN PRECURSOR TRANSMEMBRANE PD000001:Y183-E301 Tyrosine kinase catalytic domain signature PR00109:F127-L145, V199-T221, T273-A295 Eukaryotic protein kinase domain pkinaase: Y13-I299 Rgd R426-D428 Protein_Kinase_Atp L19-K42 Protein kinases signatures and profile protein_kinase_tyr.prf: H113-D164 | BLAST_PRODUM BLIMPS_PRINTS HMMER_PFAM MOTIFS MOTIFS PROFILESSCAN |
| 5 | 7474797CD1 | 328 | S18 S184 S38 S57 S62 T251 T95 | N260 | PROTEIN KINASE DOMAIN DM00004 P25389 22-275:E26-K280 Tyrosine kinase catalytic domain signature PR00109:L102-Q115, Y138-L156, S220-T242 Eukaryotic protein kinase domain pkinaase: Y25-G293 Protein_Kinase_Atp I31-K54 | BLAST_DOMO BLIMPS_PRINTS HMMER_PFAM MOTIFS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|--------------------------------------|--|---|
| 5 | | | | | Protein_Kinase_St I144-L156 Protein kinases signatures and profile protein_kinase_tyr.prf: L124-Q177 | MOTIFS PROFILESSCAN |
| 6 | 3296272CD1 | 370 | S10 S167 S230 S239 S26 S283 S285 S330 S44 S47 T209 T226 T244.T34 | N103 N165, N368 | | |
| 7 | 1989319CD1 | 1369 | S1022 S1086 S1142 S1250 S1292 S1354 S146 S277 S307 S366 S464 S551 S592 S609 S674 S695 S877 T100 T1003 T1088 T134 T288 T391 T469 T585 T613 T653 T664 T84 | N1339 N422 N607 N692 N693 N832 | Protein kinases signatures and profile protein_kinase_tyr.prf: R136-G216 PROTEIN KINASE DOMAIN DM00004 P27448 58-297: R70-R305 DM00004 I48609 55-294: R70-R305 DM00004 Q05512 55-294: R70-R305 DM00004 JCI446 20-261: E67-M308 Tyrosine kinase catalytic domain signature PR00109: T142-V155, F178-L196, V244-S266 Eukaryotic protein kinase domain: Y66-M317 Protein_Kinase_ATP-binding region signature: I72-K95 Serine/Threonine protein kinases active-site signature: I184-L196 SpScan signal_cleavage: M1-G14 | PROFILESSCAN BLAST_DOMO BLIMPS_PRINTS HMMER_PFAM MOTIFS MOTIFS SPSCAN |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|-------------------------------|---|---|
| 8 | | | S768 S772 S840 S861 S886 S91 S927 S953 T1032 T1086 T127 T1277 T1450 T1470 T1568 T1575 T1712 T1718 T1786 T1798 T1811 T1827 T1945 T2083 T2144 T2160 T2171 T2181 T2235 T2322 T2362 T2397 T241 T378 T429 T445 T593 T679 T689 T695 T789 T880 T960 Y2185 | | Protein kinase signature protein_kinase_tyr.prf: F443-V523 Tyrosine kinase catalytic domain PR00109: Y489-V507, V570-D592 PROTEIN KINASE DOMAIN DM00004 A54602 455-712: T378-G636 DM00004 S42867 75-498: I379-K522 DM08046 P05986 1-397: S374-K522, V549-D697 DM08046 P06244 1-396: D375-K522 PROTEIN KINASE SERINE/THREONINE KIN4 MICROTUBULE ASSOCIATED TESTIS SPECIFIC TESTIS SPECIFIC MAST205 PD041650: K183-D375 MICROTUBULE ASSOCIATED TESTIS SPECIFIC SERINE/THREONINE PROTEIN KINASE 205KD MAST205 KINASE PD135564: M1-Y182 PD142315: H1151-A1412, P1969-P2107 PD182663: T725-N982 Atp_Gtp_A: A1841-T1848 Protein_Kinase_St: I495-V507 | PROFILES CAN BLIMPS_PRINTS BLAST_DOMO BLAST_PROD OM BLAST_PROD OM MOTIFS MOTIFS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|---|--|--|
| 9 | 5502218CD1 | 2135 | S1189 S1641 S1651 S1714 S174 S1765 S1790 S1814 S1818 S1874 S1888 S189 S1993 S1994 S2018 S2023 S2039 S231 S260 S29 S34 S363 S378 S469 S588 S679 S819 S843 S858 S863 S879 S929 S973 T1270 T1407 T160 T1682 T1723 T1881 T1998 T243 T258 T290 T308 T373 T436 T48 T60 T625 T73 T763 T850 T851 T868 T899 T91 Y1855 Y468 | N1046 N1078 N1628 N1798 N1808 N1816 N1904 N2016 N2116 N27 N877 N89 | Eukaryotic protein kinase domain pkinase: L221-F479 Protein kinase signature protein_kinase_tyr.prf: L324-S378 Tyrosine kinase catalytic domain PR00109: T301-K314, H339-I357, V403-C425, A448-I470 PROTEIN KINASE DOMAIN DM00004 S49611 39-259: I227-V447 DM00004 P51957 8-251: I227-I470 DM00004 Q05609 553-797: E226-C459 DM00004 P41892 11-249: I227-K471 Protein Kinase_St: I345-I357 | HMNER_PFAM PROFILESKAN BLIMPS_PRINTS BLAST_DOMO MOTIFS |
| 10 | 55056054CD1 | 398 | S300 S373 S386 S62 T136 T326 T341 T37 T388 T43 T96 Y117 | N47 | Eukaryotic protein kinase domain pkinase: F91-F345 Protein kinase C terminal domain pkinase_C: A346-D377 Tyrosine kinase catalytic domain PR00109: M168-R181, Y204-I222, V267-D289 | HMNER_PFAM HMNER_PFAM BLIMPS_PRINTS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|-------------------------------|--|--|
| 10 | | | | | <p>PROTEIN KINASE DOMAIN DM00004 P00517 44-281: E92-G330 DM00004 S19028 46-283: R93-G330 DM00004 B35755 53-290: E92-G330 DM08046 P06244 1-396: T82-I387</p> <p>CAMPDEPENDENT SERINE/THREONINE PKA PROTEIN KINASE BETA2CATALYTIC CBETA2 TRANSFERASE ATPBINDING ALTERNATIVE SP PHOSPHORYLATION PD052800: M1-R61 SERINE/THREONINE TYROSINEPROTEIN KINASE TRANSFERASE PHOSPHORYLATION TRANSMEMBRANE ATPBINDING RECEPTOR PD000001: T243-F287, K94-V171, M166-V239, R104-G174, D289-F345 Protein_Kinase_Atp: L97-K120 Protein_Kinase_St: L210-I222</p> | BLAST_DOMO |
| 11 | 7481989CD1 | 929 | S147 S258 S292 S298 S337 S482 S595 S603 S612 S642 S716 S845 S916 T139 T186 T293 T387 T394 T426 T436 T48 T822 Y312 Y402 | N594 N60 | <p>Eukaryotic protein kinase domain pkinese: P652-P897</p> <p>Protein kinases signatures protein_kinase_tyr.prf: T753-K800</p> <p>Tyrosine kinase catalytic site PR00109: F767-L785, V829-A851, F877-L899</p> <p>PROTEIN KINASE DOMAIN DM00004 A56040 233-476: G655-P897 DM00004 Q05609 553-797: Q656-P897 DM00004 P51813 419-658: Q656-P897 DM00004 S60612 419-658: Q656-P897</p> <p>Protein_Kinase_Atp: L658-K681</p> | <p>MOTIFS</p> <p>MOTIFS</p> <p>HMMER_PFAM</p> <p>PROFILESSCAN</p> <p>BLIMPS_PRINTS</p> <p>BLAST_DOMO</p> <p>MOTIFS</p> |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|--|---|
| 11 | | | | | Protein_Kinase_St: L773-L785 | MOTIFS |
| 12 | 55052990CD1 | 1097 | S1017 S1023 S1034 S118 S233 S286 S541 S569 S611 S618 S648 S715 S778 S789 S816 S822 S829 S842 S888 S89 S974 T1035 T1056 T1059 T1083 T112 T145 T304 T373 T404 T405 T446 T565 T72 T785 T892 T964 T970 Y335 | N1015 N821 N870 | Eukaryotic protein kinase domain pkinae: L144-L403 SH3 domain SH3: P55-R114 Protein kinase signature protein_kinase_tyr.prf: L242-T305 Receptor tyrosine kinase class II BL00239: E191-P238, L355-I399 Receptor tyrosine kinase class III BL00240: E300-V347, V347-I399 Tyrosine kinase catalytic domain PR00109: M220-S233, D258-I276, G311-I321, S330-I352, C374-F396 SH3 domain signature PR00452: P55-A65, D69-K84, D91-N100, R102-R114 PROTEIN KINASE DOMAIN DM00004 A53800 119-368: L146-F396 DM00004 I38044 100-349: L146-F396 DM00004 JC2363 126-356: W163-F396 ZIPPER MOTIF LEUCINE DM08113 I38044 392-721: R438-A749, P869-P893 KINASE DOMAIN SH3 MIXED LINEAGE SERINE/THREONINE WITH LEUCINE ZIPPER PD024997: I406-A749, F419-E833 PD034700: N855-R966, P934-P1022 | HMMER_PFAM HMMER_PFAM PROFILES SCAN BLIMPS_BLOCKS BLIMPS_BLOCKS BLIMPS_PRINTS BLIMPS_PRINTS BLAST_DOMO BLAST_DOMO BLAST_PRODOM |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|----------------------------------|---|--|
| 12 | | | | | SERINE/THREONINE PROTEIN TYROSINE KINASE TRANSFERASE ATP-BINDING PHOSPHORYLATION RECEPTOR PRECURSOR TRANSMEMBRANE PD000001: L146-F222, W315-F349, L242-A317 Protein_Kinase_Atp: I150-K171 Protein_Kinase_St: I264-I276 signal_cleavage: M1-A17 | BLAST_PRODUM MOTIFS MOTIFS SPSCAN |
| 13 | 7482377CD1 | 928 | S121 S147 S150 S155 S212 S258 S293 S298 S332 S336 S340 S347 S355 S368 S380 S422 S552 S600 S625 S659 S690 S726 S729 S744 S787 S802 S814 S865 S893 S914 S915 T14 T262 T353 T447 T468 T491 T506 T597 T672 T730 T779 T818 T826 T832 T840 T97 Y488 | N256 N260 N445 N550 N755 N77 N95 | GUANYLATE KINASE DM00755 Q07157 628-788: E623-A780 DM00755 I38757 709-898: L670-W778 PDZ domain PDZ: T20-P101, S204-D280, R391-K471 GLGF DOMAIN DM00224 Q07157 1-94: M10-K99 DM00224 Q07157 402-488: P388-Q469 PDZ domain PF00595: I429-N439 Domain present in ZO-1 PF00791: I413-A451, L456-S498 TIGHT JUNCTION PROTEIN ZO2 ISOFORM ZO1 SH3 DOMAIN ALTERNATIVE SPLICING PD011344: R470-F626 PD021419: T730-D881 ZO3 PD068424: F101-Q222 PD072431: F284-V392 Leucine zipper: L733-L754 | HMMER_PPFAM BLAST_DOMO HMMER_PPFAM BLAST_DOMO BLIMPS_PPFAM BLIMPS_PPFAM BLAST_PRODUM BLAST_PRODUM MOTIFS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|--|---|
| 13 | | | | | Rgd: R507-D509 | MOTIFS |
| 14 | 7758364CD1 | 766 | S109 S129 S134 S182 S23 S3 S312 S334 S347 S484 S532 S623 S67 S710 S724 S93 T133 T173 T331 T389 T416 T461 T488 T542 T666 T693 T739 T760 | N164 N619 N681 | Eukaryotic protein kinase domain pkinae: Y394-V651 Protein kinase signature protein_kinase_tyr.prf: D491-L548 Tyrosine kinase catalytic domain PR00109: M469-T482, Y505-V523, V572-E594 PROTEIN KINASE DOMAIN DM00004 S57347 21-266: V399-T641 DM00004 JU0270 16-262: I396-A642 DM00004 A44412 16-262: I396-A642 DM00004 P11798 15-261: I400-A642 LISSENCEPHALINX ISOFORM DOUBLECORTIN PD024506: I7-N322 Protein_Kinase_Atp: I400-K423 Protein_Kinase_St: I511-V523 signal_cleavage: M1-A56 PROTEIN T13D8.31 KINASE PANTOTHENATE TRANSFERASE D9719.34P CODED FOR BY C. ELEGANS PD018089: L93-L441 Tyrosine protein kinases specific active-site signature: A159-R208 | MOTIFS HMMER_PFAM PROFILES SCAN BLIMPS_PRINTS BLAST_DOMO BLAST_PROD OM MOTIFS MOTIFS SPSCAN BLAST_PROD OM PROFILES SCAN |
| 15 | 5850001CD1 | 447 | S121 S124 S23 S246 S316 S320 S362 S428 S45 S80 T111 T204 T286 T306 T307 T321 T59 | N180 | | |
| 16 | 7477062CD1 | 348 | S169 S19 S316 S99 T224 T28 T80 Y62 | | | |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---------------------------------|-------------------------------|---|----------------------------------|
| 16 | | | | | PROTEIN KINASE DOMAIN DM08046 P06244 1-396: G3-W263 DM00004 B35755 53-290: E63-L267 DM00004 P22216 200-456: L68-S316 DM00004 P06245 72-308: V65-W263 | BLAST_DOMO |
| | | | | | KINASE PROTEIN TRANSFERASE ATP-BINDING SERINE/THREONINE PROTEIN PHOSPHORYLATION RECEPTOR TYROSINE PROTEIN PRECURSOR TRANSMEMBRANE PD000001: A225-F273, Q166-V191, Y62-R97 | BLAST_PRODROM |
| | | | | | Tyrosine kinase catalytic domain PR00109: T137-Q150, Y173-V191, L244-P266 Eukaryotic protein kinase domain: Y62-R315 | BLIMPS_PRINTS HMMER_PFAM |
| | | | | | Protein kinases ATP-binding region signature: L68-K91 | MOTIFS |
| | | | | | Serine/Threonine protein kinases active-site signature: L179-V191 | MOTIFS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|--|--|
| 17 | 7477207CD1 | 341 | S100 S133 S180 S299 S31 S337 S59 T175 T185 T235 T255 T261 | N141 N89 | Eukaryotic protein kinase domain: Y8-L325 Tyrosine protein kinases specific active-site signature: T140-S200 PROTEIN KINASE DOMAIN DM00004 P39009 202-470: R110-L251 DM00004 Q02723 16-259: E104-V196 DM00004 P08414 44-285: V118-V196 DM00004 P23572 6-277: L115-K195 KINASE PROTEIN TRANSFERASE ATP-BINDING SERINE/THREONINE PROTEIN PHOSPHORYLATION RECEPTOR TYROSINE PROTEIN PRECURSOR TRANSMEMBRANE PD000001: F144-A236 Tyrosine kinase catalytic domain PR00109: M119-L132, F154-I172 transmembrane domain: A238-D258 Serine/Threonine protein kinases active-site signature: I160-I172 Protein kinases ATP-binding region signature: V14-K37 | HMMER_PPFAM PROFILES SCAN BLAST_DOMO BLAST_PROD OM BLIMPS_PRINTS HMMER MOTIFS MOTIFS PROFILES SCAN |
| 18 | 4022651CD1 | 664 | S123 S166 S290 S320 S342 S383 S423 S431 S477 S485 S508 S541 S565 S615 S631 S95 T110 T256 T439 T447 T497 T590 T652 Y591 | | Protein kinases signatures and profile: E113-S166 | PROFILES SCAN |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---------------------------------|-------------------------------|--|----------------------------------|
| 118 | | | | | <p>PROTEIN KINASE DOMAIN</p> <p>DM00004 P34244 82-359:V36-T256</p> <p>DM00004 JC1446 20-261:R16-L257</p> <p>DM00004 P54645 17-258:L17-L257</p> <p>DM00004 A53621 18-258:L17-L257</p> <p>HRPOP1 F15A2.6 PROTEIN, Protein Kinase PD039115: P278-N503, PD039117: W517-E623</p> <p>Tyrosine kinase catalytic domain signature PR00109: L91-V104, F127-L145, A193-ID215</p> <p>Eukaryotic protein kinase domain: Y15-Y266</p> <p>Protein Kinases ATP-binding region signature: L21-R44</p> <p>Serine/Threonine protein kinases active-site signature: T133-T145</p> | BLAST_DOMO |
| | | | | | BLAST_PRODOM | |
| | | | | | BLIMPS_PRINTS | |
| | | | | | HMMER_PPFAM | |
| | | | | | MOTIFS | |
| | | | | | MOTIFS | |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|--|---|
| 19 | 7274927CD1 | 177 | S19 T111 T128 | | Nucleoside diphosphate kinases active site: N120-T168 NUCLEOSIDE DIPHOSPHATE KINASES DM00773 I39074 19-168: E30-E177 DM00773 P48817 3-152: E30-E177 DM00773 P50590 1-150: E30-E177 DM00773 Q07661 1-148: E30-E177 KINASE DIPHOSPHATE NUCLEOSIDE TRANSFERASE NDK NDP ATP-BINDING PROTEIN I PRECURSOR PD001018: E30-E177 Nucleoside diphosphate kinases proteins BL00469: W103-L157 Nucleoside diphosphate kinases ND: E30-E177 Nucleoside diphosphate kinases active site: N140-V148 SpScan signal_cleavage: M1-G15 | PROFILES SCAN BLAST_DOMO BLAST_PRODOR BLIMPS_BLOCKS HMME PFAM MOTIFS SPSCAN |
| 20 | 7946584CD1 | 396 | S193 S194 S230 S6 S89 T122 T212 T45 T5 | N4 N43 | Protein kinases signatures and profile: T122-E174 Eukaryotic protein kinase domain: F23-M281 PROTEIN KINASE DOMAIN DM00004 P54644 122-362: I25-S270 DM08046 P05986 1-397: D13-P300 DM00004 P28178 155-393: I25-R268 DM08046 P06244 1-396: F23-P300 Tyrosine kinase catalytic domain signature PR00109: V100-Q113, Y136-L154, V204-R226 | PROFILES SCAN HMME PFAM BLAST_DOMO BLIMPS_PRINTS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|--|--|
| 20 | | | | | Protein kinases ATP-binding region signature: I29-K52 Serine/Threonine protein kinases active-site signature: I142-L154 | MOTIFS |
| 21 | 8088078CD1 | 614 | S292 S295 S518 S525 S574 S578 T27 T389 T418 T499 T92 | N309 N595 N598 | C2 domain signature and profile: G39-V93 C2-DOMAIN DM00150 P05129 150-278: G39-L159 DM00150 P13677 186-313: G39-L159 PROTEIN KINASE C ALPHA DM04692 P05130 1-638: G39-G164 DM04692 A37237 1-676: G39-G164 C2 domain signature PR00360: Q66-L78, D95-P108 C2 domain C2: L52-S139 PDZ domain (Also known as DHR or GLGF). PDZ: Q199-M275 ATP/GTP-binding site motif A (P-loop): G395-S402 Eukaryotic protein kinase domain: L44-C282 PROTEIN KINASE DOMAIN DM00004 P51954 6-248: D50-P271 DM00004 P51957 8-251: V42-P271 DM00004 Q08942 22-269: D50-P271 DM00004 P51955 10-261: R47-P271 Tyrosine kinase catalytic domain PR00109: M104-Q117 H142-L160 S208-A230 Y251-L273 Protein kinases signatures and profile: I129-S182 | MOTIFS PROFILES CAN BLAST_DOMO BLAST_DOMO BLIMPS_PRINTS HMMER_PFAM HMMER_PFAM MOTIFS HMMER_PFAM BLAST_DOMO BLIMPS_PRINTS PROFILES CAN |
| 22 | 2674269CD1 | 484 | S122 S179 S222 S248 S295 S422 S445 T111 T27 T437 T65 | | | |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|--|-------------------------------|---|----------------------------------|
| 22 | | | | | Serine/Threonine protein kinases active-site signature: I148-L160 | MOTIFS |
| 23 | 7472409CD1 | 460 | S155 S198 S224 S271 S398 S421 S98 T41 T413 T87 | | Eukaryotic protein kinase domain: Y4-C258 PROTEIN KINASE DOMAIN DM00004 P51954 6-248: R6-P247 DM00004 P51957 8-251: I7-P247 DM00004 Q08942 22-269: V9-P247 DM00004 P11837 13-285: I124-P247, V10-H120 | HMMER_PFAM BLAST_DOMO |
| | | | | | Tyrosine kinase catalytic domain PR00109: M80-Q93 H118-L136 S184-A206 Y227-L249 Protein kinases signatures and profile: I105-S158 | BLIMPS_PRINTS PROFILES SCAN |
| | | | | | Protein kinases ATP-binding region signature: V10-K33 | MOTIFS |
| | | | | | Serine/Threonine protein kinases active-site signature: I124-L136 | MOTIFS |

Table 3 (cont.)

| SEQ ID NO: | Incyte Polypeptide ID | Amino Acid Residues | Potential Phosphorylation Sites | Potential Glycosylation Sites | Signature Sequences, Domains and Motifs | Analytical Methods and Databases |
|------------|-----------------------|---------------------|---|-------------------------------|---|--|
| 24 | 7477484CD1 | 1413 | S1016 S1082 S118 S1269 S1285 S1295 S355 S400 S413 S471 S528 S547 S608 S649 S746 S818 S96 T1003 T1041 T1350 T279 T339 T467 T834 T880 T968 T995 Y185 Y748 | N1034 N1358 | Tyrosine protein kinases specific active-site signature: Y262-L274 signal_cleavage: M1-A20 PROTEIN KINASE DOMAIN DM00004 S23008 273-531: Q137-S400 DM00004 P06213 1024-1282: L136-S400 DM00004 P15209 538-798: Q137-R398 DM00004 P08069 1000-1258: Q137-S400 APOPTOSIS ASSOCIATED TYROSINE KINASE KIAA0641 PROTEIN PD148361: P1080-P1376 APOPTOSIS ASSOCIATED TYROSINE KINASE PD059222: L56-Y135 Kinase Protein Domain PD00584: L136-G145 Tyrosine kinase catalytic domain PR00109: H256-L274 I305-L315 S331-H353 Y380-S402 M210-R223 Protein kinases signatures and profile: T242-E294 Receptor tyrosine kinase class II signature: R270-E317 signal peptide: M1-A20 Eukaryotic protein kinase domain: L133-L404 Protein kinases ATP-binding region signature: I139-K164 | MOTIFS SPSCAN BLAST_DOMO BLAST_PRODOME BLIMPS_BLOCKS BLIMPS_PRINTS PROFILES SCAN PROFILES SCAN HMMER HMMER_PPAM MOTIFS |

Table 4

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|---------------------|-------------|-------------|
| 25 | 7312543CB1 | 2060 | 1-367, 1981- 2060, 1721-1882, 1406-1638, 625- 1129 | GBI.G9101216_802181 | 961 | 1719 |
| | | | | 5J1_8024094J1_edit | | |
| | | | | 55067455J1 | 1 | 617 |
| | | | | FL7312543 | 1473 | 1716 |
| | | | | 71899371V1 | 448 | 986 |
| | | | | 6259135F8 | 1891 | 2060 |
| | | | | (BMARTXT06) | | |
| | | | | 8024094J1 | 920 | 1609 |
| | | | | (BRABDIE02) | | |
| | | | | 7084221H1 | 3331 | 3859 |
| 26 | 7477427CB1 | 5694 | 1807-4876, 1-869 | (STOMTMR02) | | |
| | | | | 3081175H1 | 5209 | 5518 |
| | | | | (BRAIUNT01) | | |
| | | | | 7341442H1 | 2311 | 2964 |
| | | | | (COLNDIN02) | | |
| | | | | 6053208J1 | 4727 | 5119 |
| | | | | (BRABDIR03) | | |
| | | | | 6051790H1 | 3609 | 4274 |
| | | | | (BRABDIR03) | | |
| | | | | 452790T6 | 1146 | 1795 |
| | | | | (TLYMNOT02) | | |
| | | | | 1340485F6 | 1 | 601 |
| | | | | (COLNTUT03) | | |
| | | | | 6051790J1 | 4347 | 4900 |
| | | | | (BRABDIR03) | | |
| | | | | 5048724H1 | 1016 | 1275 |
| | | | | (BRSTNOT33) | | |
| | | | | 4954623H1 | 504 | 787 |
| | | | | (ENDVUNT01) | | |
| | | | | 55099289J1 | 1599 | 2178 |
| | | | | G1441460 | 570 | 809 |
| | | | | 6355285H1 | 828 | 1103 |
| | | | | (LUNGDIS03) | | |
| | | | | 2818149F6 | 5251 | 5694 |
| | | | | (BRSTNOT14) | | |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|--------------------------|-------------|-------------|
| 26 | | | | 6800667F6 (COLENOT03) | 2049 | 2603 |
| | | | | 6322587F7 (LUNGDI02) | 3892 | 4570 |
| | | | | 5735737F6 (KIDCTMT01) | 4818 | 5470 |
| | | | | 6771396J1 (BRAUNOR01) | 3245 | 3857 |
| | | | | 6800667R6 (COLENOT03) | 2727 | 3335 |
| 27 | 7481495CB1 | 3520 | 1-40, 2862-3520, 1622-1689, 607- 1074 | 71125065V1 | 2970 | 3520 |
| | | | | 71124933V1 | 2555 | 3203 |
| | | | | 71124726V1 | 1649 | 2196 |
| | | | | 55143095J1 | 1 | 476 |
| | | | | 6273371F8 (BRAIFEN03) | 2069 | 2812 |
| | | | | 7289965F8 (BRAIFER06) | 209 | 841 |
| | | | | GBI.g9755986_edit_1 | 1151 | 3394 |
| | | | | GBI.g9755986_edit_3 | 498 | 1231 |
| 28 | 55053189CB1 | 1988 | 1-1067 | 71911787V1 | 280 | 990 |
| | | | | 6959111H1 (SKINDIA01) | 1196 | 1852 |
| | | | | 71910755V1 | 1249 | 1959 |
| | | | | 2222335T6 (LUNGNOT18) | 1464 | 1988 |
| | | | | 55053117J1 | 1 | 491 |
| | | | | 71911607V1 | 547 | 1228 |
| 29 | 7474797CB1 | 1822 | 1-470, 963-1217 | GNN.g6850939_002 | 738 | 1734 |
| | | | | 55078203J1 | 135 | 920 |
| | | | | 55078259J1 | 1 | 917 |
| | | | | 93405101 | 1507 | 1822 |
| 30 | 3296272CB1 | 1814 | 1-34 | 8050406H1 (LUNGUS02) | 724 | 1394 |
| | | | | 3296272F6 (TLVJINT01) | 52 | 723 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|--|--|--|---|
| 30 | | | | GNN.g7711609.edit1 8010594H1 (NOSEDIC02) 4550262T1 (HELAUNT01) | 124 1 1179 | 1246 473 1814 |
| 31 | 1989319CB1 | 4381 | 1-606, 1171- 2589, 3359-3731, 4352-4381, 3137- 3182 | 6766365H1 (BRAUNOR01) 6771934J1 (BRAUNOR01) 7081255H1 (STOMTMR02) 7074415H1 (BRAUTDR04) 7233628H1 (BRAXTDRI5) 2972522F6 (HEAONOT02) 3550738T6 (SYNONOT01) 7689848H1 (PROSTME06) 7643518H1 (SEMTIDE01) 55056624J1 GNN.g7139740_000020 _002.edit 6772392H1 (BRAUNOR01) 7641909J1 (SEMTIDE01) 7039379H1 (UTRSTMR02) 5965355H1 (BRATNOT05) | 3988 1284 1899 7 3192 3805 3467 1200 2454 191 1 670 1390 2393 2998 | 4381 1867 2467 546 3760 4374 4338 1856 3131 833 273 1296 2054 2982 3635 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|---|---|--|
| 32 | 079284CB1 | 7862 | 6343-7041, 1043- 1581, 1-453, 2297-6211 | 6558834H1 (BRAFNON02) 6957453H1 (BLADNOR01) 7030154F6 (BRAXTDR12) 2696941F6 (UTRSNOT12) 6993445H1 (BRAQTDR02) 6315055H1 (NERDTDN03) 7183303H1 (BONRFEC01) 55032462H1 1005113H1 (BRSTNOT03) 7034608H1 (SINTFER03) 55032462J1 92224546_CD 7740563H1 (THYMN0E01) 6943723H1 (FTTUTUR01) 7764524H1 (URETTUE01) 7030154R6 (BRAXTDR12) 6493861H1 (MIXDUNB01) 7764524J1 (URETTUE01) 55111711H1 | 6806 3532 3084 6628 2679 5981 5329 4893 2531 5826 4430 1221 4113 1062 545 2885 7457 350 1 | 7501 4226 3666 7209 3284 6672 5878 5540 2782 6570 5048 7714 4788 1416 1132 3416 7862 868 520 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|---|---|---|
| 33 | 5502218CB1 | 7280 | 1-658, 1289- 3582, 6450-7280, 4416-5337 | 71172233V1 7755001H1 (SPLNTUE01) 71172416V1 7143606H1 (LIVRDIT07) 8262215J1 (MIXDUNL12) 71728206V1 1513828F6 (PANCYTUT01) 5504851F6 (BRADDIR01) 71255229V1 7099033H2 (BRAWTDR02) 7381635H1 (ENDMUNE01) 6775620H1 (OVARDIR01) 6773092H1 (BRAUNOR01) 1852020T6 (LUNGFET03) 71974333V1 6246863H1 (TESTNOT17) 71174478V1 7751827J1 (HEAONOE01) 7733935J2 (COLDDIE01) 6771926J1 (BRAUNOR01) 71088884V1 | 5856 4757 5347 2638 4008 6354 1481 2190 2770 3321 4401 1 4072 6862 823 1346 5283 1888 5932 629 3416 | 6502 5331 5905 3173 4571 7056 2005 2722 3388 3964 5070 576 4748 7280 1394 1961 5874 2490 6548 1285 4074 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|---|-------------|-------------|
| 33 | | | | 7437887H1 (ADRETUE02) | 128 | 705 |
| | | | | 7032601H1 (BRAXTDR12) | 6540 | 7193 |
| 34 | 55056054CB1 | 1260 | 817-1260 | 6391212H1 (LJNPTMC01) | 64 | 334 |
| | | | | GBI.98516102_000009 _000010_000008.edit. | 1 | 1260 |
| | | | | 55076825J1 | 1 | 132 |
| 35 | 7481989CB1 | 3161 | 1-481, 1210-2220 | 70464274V1 | 2196 | 2774 |
| | | | | 70467406V1 | 2110 | 2701 |
| | | | | 7185326H1 (BONRFEC01) | 793 | 1415 |
| | | | | 7077190R8 (BRAUTDR04) | 1 | 674 |
| | | | | 70980877V1 | 1389 | 2032 |
| | | | | 55013474H1 (GPCRDNV60) | 1517 | 2149 |
| | | | | 70464964V1 | 2517 | 3161 |
| | | | | 71292191V1 | 518 | 1150 |
| 36 | 55052990CB1 | 3538 | 1-251, 1163- 1869, 2604-3538, 695-858 | FL55052990_g4156209 _g758593 | 1 | 3294 |
| | | | | 7580350H1 (BRAIFEC01) | 3068 | 3538 |
| | | | | 6931355H1 (SINTMR01) | 1317 | 1950 |
| 37 | 7482377CB1 | 3047 | 1-1419, 3022- 3047 | 60203980U1 | 1971 | 2648 |
| | | | | 5871544H1 (COLTDT04) | 2745 | 3043 |
| | | | | g2053163 | 2589 | 3047 |
| | | | | 6821548H1 (SINTNOR01) | 1691 | 2351 |
| | | | | 7171378H1 (BRSTTMC01) | 528 | 1120 |
| | | | | 1428568F6 (SINTBST01) | 2547 | 3019 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|--------------------------------|----------------------------------|-------------|-------------|
| 37 | | | | 1625022F6 (COLNPT01) | 1053 | 1538 |
| | | | | 6822009J1 (SINTNOR01) | 1 | 666 |
| | | | | 8010427H1 (NOSEDIC02) | 693 | 1191 |
| 38 | 7758364CB1 | 2667 | 2375-2667, 702- 1754, 1-178 | 7042389H1 (UTRSTR02) | 1 | 445 |
| | | | | 6620147H1 (BRAUDIR01) | 1777 | 2400 |
| | | | | 55137902J1 | 89 | 943 |
| | | | | 72053219V1 | 1961 | 2667 |
| | | | | 55053087J1 | 909 | 1802 |
| | | | | 7198790F8 (LUNGFER04) | 1091 | 1812 |
| 39 | 5850001CB1 | 1719 | 1108-1719 | 1773374R6 (MENTUNON3) | 1016 | 1417 |
| | | | | 2746336T6 (LUNGTUT11) | 1080 | 1719 |
| | | | | 8081565H1 (EMARTXN03) | 1 | 316 |
| | | | | 2746336F6 (LUNGTUT11) | 795 | 1320 |
| | | | | 6768690J1 (BRAUNOR01) | 324 | 914 |
| | | | | 4403478H1 (PROSDIT01) | 218 | 460 |
| 40 | 7477062CB1 | 1156 | 683-1156, 1-194, 472-644 | 8124387H1 (HEAONOC01) | 55 | 692 |
| | | | | 55149655J1 | 1 | 562 |
| | | | | GNN.g7191033_000008 _002.edit | 108 | 1156 |
| | | | | 982271H1 (TONGTUT01) | 1044 | 1156 |
| 41 | 7477207CB1 | 1096 | 923-1096 | 6882293J1 (BRAHTR03) | 1030 | 1096 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|--|---|--|
| 41 | | | | 55142304H1 GNN:g10045521_00000 3_004 | 1 65 | 782 1090 |
| 42 | 4022651CB1 | 2647 | 1-29, 2556-2647, 2233-2392, 795- 1365 | 6559541F8 (BRAFNON02) GBI:g9739340_000017 _000001_000005.edit 6149427H1 (BRANDIT03) 6559066F8 (BRAFNON02) 6951446H1 (BRAITDR02) 7228092H1 (BRAXTDRI5) 7947344H1 (BRABNOE02) 70581831V1 70590694V1 71928043V1 55071303H1 7338592T6 (SINTNON02) 6885143F6 (BRAHTDR03) g1482596 GBI:g10040007_14_ed it2 71113779V1 FL8088078_g9801056_ 000005_g6707837_1_1 -2 8088078F6 (BLADTUN02) GBI:g10040007_1_edi t | 1619 1 2099 1356 676 621 79 1 186 529 1 884 250 537 1 754 388 110 461 | 2410 178 2647 2049 1375 1060 645 700 864 1231 353 1594 960 981 160 1440 541 527 1845 |
| 43 | 7274927CB1 | 864 | 1-31, 822-864 | | | |
| 44 | 7946584CB1 | 1594 | 1-199, 1369-1594 | | | |
| 45 | 8088078CB1 | 1845 | 1-114, 1011-1845 | | | |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|---|--------------------------|-------------|-------------|
| 46 | 2674269CB1 | 1680 | 1-203, 991-1147 | 6248538F8 (LUNPTUT02) | 1288 | 1680 |
| | | | | 3156348F6 (TLYMTXT02) | 1125 | 1403 |
| | | | | GBI.g7321523_edit | 220 | 957 |
| | | | | 55074191J1 | 1 | 217 |
| | | | | 2674269H1 (KIDNNOT19) | 969 | 1213 |
| | | | | 7990470H2 | 209 | 851 |
| | | | | (UTRCDIC01) | | |
| 47 | 7472409CB1 | 1528 | 1354-1528, 849-1005 | 3926891H1 (KIDNNOT19) | 19 | 291 |
| | | | | 6248538F8 (LUNPTUT02) | 1146 | 1528 |
| | | | | 3156348F6 (TLYMTXT02) | 983 | 1261 |
| | | | | GBI.g7321523_edit | 78 | 815 |
| | | | | 2674269H1 (KIDNNOT19) | 827 | 1071 |
| | | | | 7990470H2 | 1 | 709 |
| | | | | (UTRCDIC01) | | |
| 48 | 7477484CB1 | 4988 | 4651-4742, 3382-4011, 1-491, 4429-4477, 1495-3210, 1074-1222, 4361-4388 | 7259537F6 (BRAWNOC01) | 2988 | 3998 |
| | | | | 4456665F8 (HEAADIR01) | 2819 | 3339 |
| | | | | 7087893H1 (BRAUTDR03) | 2095 | 2275 |
| | | | | FL7477484_g9690314_ | 800 | 1040 |
| | | | | g3327096_1_1-2 | | |
| | | | | 6763489J1 (BRAUNOR01) | 965 | 1524 |
| | | | | 7226615H1 (BRAXTDR15) | 206 | 721 |
| | | | | 6770515H1 (BRAUNOR01) | 1 | 510 |

Table 4 (cont.)

| Polynucleotide SEQ ID NO: | Incyte Polynucleotide ID | Sequence Length | Selected Fragment(s) | Sequence Fragments | 5' Position | 3' Position |
|------------------------------|-----------------------------|--------------------|-------------------------|---|-------------|-------------|
| 48 | | | | 6979719H1 (BRAHTDR04) | 4239 | 4801 |
| | | | | 6770515R8 (BRAUNOR01) | 1394 | 2240 |
| | | | | 3825546H1 (BRAHCT02) | 4593 | 4988 |
| | | | | FL7477484_g9690314_ g3327096_1_5-6 | 1248 | 1845 |
| | | | | 2570231T6 (HIPOAZT01) | 4505 | 4955 |
| | | | | FL7477484_g9690314_ g3327096_1_15-16 | 3868 | 4333 |
| | | | | GNN.g9690314_008 | 247 | 4488 |
| | | | | | | |

Table 5

| Polynucleotide SEQ ID NO: | Incyte Project ID | Representative Library |
|------------------------------|----------------------|------------------------|
| 25 | 7312543CB1 | BRABDIE02 |
| 26 | 7477427CB1 | THYMNOR02 |
| 27 | 7481495CB1 | BRAIFER06 |
| 28 | 55053189CB1 | LUNGNOT18 |
| 29 | 7474797CB1 | MIXDUNB01 |
| 30 | 3296272CB1 | CERVNOT01 |
| 31 | 1989319CB1 | BRAUNOR01 |
| 32 | 079284CB1 | UTRSNOT12 |
| 33 | 5502218CB1 | BRAUNOR01 |
| 34 | 55056054CB1 | LUNPTMC01 |
| 35 | 7481989CB1 | BLADNOT05 |
| 36 | 55052990CB1 | BNARUNR02 |
| 37 | 7482377CB1 | SINTNOR01 |
| 38 | 7758364CB1 | LUNGFER04 |
| 39 | 5850001CB1 | LUNGUT11 |
| 40 | 7477062CB1 | TONGTUT01 |
| 41 | 7477207CB1 | SINTFEE02 |
| 42 | 4022651CB1 | BRANDIT03 |
| 43 | 7274927CB1 | MYEPTXT02 |
| 44 | 7946584CB1 | BRAHTDR03 |
| 45 | 8088078CB1 | ENDINOT02 |
| 46 | 2674269CB1 | TLYMTXT02 |
| 47 | 7472409CB1 | TLYMTXT02 |
| 48 | 7477484CB1 | BRAUNOR01 |

Table 6

| Library | Vector | Library Description |
|-----------|----------|--|
| BLADNOT05 | PINCY | Library was constructed using RNA isolated from bladder tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology for the associated tumor tissue indicated grade 3 transitional cell carcinoma. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use. |
| BMARUNR02 | PIGEN | This random primed library was constructed using RNA isolated from an untreated SH-SY5Y cell line derived from bone marrow neuroblastoma tumor cells removed from a 4-year-old Caucasian female. |
| BRABDIE02 | PINCY | This 5' biased random primed library was constructed using RNA isolated from diseased cerebellum tissue removed from the brain of a 57-year-old Caucasian male who died from a cerebrovascular accident. Serologies were negative. Patient history included Huntington's disease, emphysema, and tobacco abuse (3-4 packs per day, for 40 years). |
| BRAHTDR03 | PCDNA2.1 | This random primed library was constructed using RNA isolated from archaectortex, anterior hippocampus tissue removed from a 55-year-old Caucasian female who died from cholangiocarcinoma. Pathology indicated mild meningeal fibrosis predominately over the convexities, scattered axonal spheroids in the white matter of the cingulate cortex and the thalamus, and a few scattered neurofibrillary tangles in the entorhinal cortex and the periaqueductal gray region. Pathology for the associated tumor tissue indicated well-differentiated cholangiocarcinoma of the liver with residual or relapsed tumor. Patient history included cholangiocarcinoma, post-operative Budd-Chiari syndrome, biliary ascites, hydrothorax, dehydration, malnutrition, oliguria and acute renal failure. Previous surgeries included cholecystectomy and resection of 85% of the liver. |
| BRAIFER06 | PCDNA2.1 | This random primed library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who was stillborn with a hypoplastic left heart at 23 weeks' gestation. Serologies were negative. |
| BRANDIT03 | PINCY | Library was constructed using RNA isolated from pineal gland tissue removed from a 79-year-old Caucasian female who died from pneumonia. Neuropathology indicated severe Alzheimer Disease, moderate to severe arteriolosclerosis of the intracranial blood vessels, moderate cerebral amyloid angiopathy and infarctions involving the parieto-occipital lobes. There was atrophy of all lobes, caudate, putamen, amygdala, hippocampus, vermis, optic nerve, and the cerebral cortical white matter. There was cystic cavitation in the left medial occipital lobe, the right posterior parietal region, the right side insular cortex, and the right occipital and inferior parietal lobes. The ventricular system was severely dilated. Stains show numerous diffuse as well as neuritic amyloid plaques |

Table 6 (cont.)

| Library | Vector | Library Description |
|-----------|---------|--|
| BRAUNOR01 | pINCY | <p>throughout all neocortical areas examined. There were numerous neurofibrillary tangles predominantly in the pyramidal cell neurons of layers 3 and 5, however, small interneurons in layers 3, 4, and 6 also contain tangles. The caudate and putamen contain large areas of mineralization and scattered neurofibrillary tangles. The amygdala was markedly gliotic containing numerous neurofibrillary, argyrophilic and ghost type tangles; and scattered cells with granulovacuolar degeneration and focal cells with Lewy-like body inclusions. The hippocampus contains marked gliosis with complete loss of pyramidal cell neurons in the CA1 region. Silver stained sections show numerous neuritic plaques and scattered neurofibrillary tangles within the dentate gyrus, CA2, and CA3 regions. The substantia nigra shows numerous neurofibrillary tangles in the periaqueductal grey region. Patient history included gastritis with bleeding, glaucoma, PVD, COPD, delayed onset tonic/clonic seizures, transient ischemic attacks, pseudophakia, and allergies to aspirin and clindamycin. Family history included Alzheimer disease.</p> <p>This random primed library was constructed using RNA isolated from striatum, globus pallidus and posterior putamen tissue removed from an 81-year-old Caucasian female who died from a hemorrhage and ruptured thoracic aorta due to atherosclerosis. Pathology indicated moderate atherosclerosis involving the internal carotids, bilaterally; microscopic infarcts of the frontal cortex and hippocampus; and scattered diffuse amyloid plaques and neurofibrillary tangles, consistent with age. Grossly, the leptomeninges showed only mild thickening and hyalinization along the superior sagittal sinus. The remainder of the leptomeninges was thin and contained some congested blood vessels. Mild atrophy was found mostly in the frontal poles and lobes, and temporal lobes, bilaterally. Microscopically, there were pairs of Alzheimer type II astrocytes within the deep layers of the neocortex. There was increased satellitosis around neurons in the deep gray matter in the middle frontal cortex. The amygdala contained rare diffuse plaques and neurofibrillary tangles. The posterior hippocampus contained a microscopic area of cystic cavitation with hemosiderin-laden macrophages surrounded by reactive gliosis. Patient history included sepsis, cholangitis, post-operative atelectasis, pneumonia CAD, cardiomegaly due to left ventricular hypertrophy, splenomegaly, arteriolonephrosclerosis, nodular colloidal goiter, emphysema, CHF, hypothyroidism, and peripheral vascular disease.</p> |
| CERVNOT01 | ESPORT1 | <p>Library was constructed using RNA isolated from the uterine cervical tissue of a 35-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. Pathology indicated mild chronic cervicitis. Family history included atherosclerotic coronary artery disease and type II diabetes.</p> |

Table 6 (cont.)

| Library | Vector | Library Description |
|-----------|----------|--|
| ENDINOT02 | pINCY | The library was constructed using RNA isolated from treated iliac artery endothelial cells removed from a Black female. The cells were treated with TNF alpha 10ng/ml and IL-1 beta 10ng/ml for 20 hours. |
| LUNGFER04 | PCDNA2.1 | This random primed library was constructed using RNA isolated from lung tissue removed from a Caucasian male fetus who died from fetal demise. |
| LUNGNOT18 | pINCY | Library was constructed using RNA isolated from left upper lobe lung tissue removed from a 66-year-old Caucasian female. Pathology for the associated tumor tissue indicated a grade 2 adenocarcinoma. Patient history included cerebrovascular disease, atherosclerotic coronary artery disease, and pulmonary insufficiency. Family history included a myocardial infarction and atherosclerotic coronary artery disease. |
| LUNGTUT11 | pINCY | Library was constructed using RNA isolated from lung tumor tissue removed from the right lower lobe a 57-year-old Caucasian male during a segmental lung resection. Pathology indicated an infiltrating grade 4 squamous cell carcinoma. Multiple intrapulmonary peribronchial lymph nodes showed metastatic squamous cell carcinoma. Patient history included a benign brain neoplasm and tobacco abuse. Family history included spinal cord cancer, type II diabetes, cerebrovascular disease, and malignant prostate neoplasm. |
| LUNPTMC01 | pINCY | This large size-fractionated library was constructed using RNA isolated from pleura tissue removed from a 58-year-old Caucasian female during segmental lung resection. Pathology for the matched tumor tissue indicated metastatic grade 4 leiomyosarcoma, forming a mass in the left lower lobe lung, with extension into the lumen of the pulmonary vein. Patient history included a malignant retroperitoneum neoplasm with metastasis to lung, an unspecified respiratory abnormality, cough, hyperlipidemia, paralytic polio, benign bladder neoplasm, normal delivery, benign hypertension, and tobacco abuse in remission. Family history included benign hypertension, hyperlipidemia skin cancer, and cerebrovascular disease. |
| MIXDUNB01 | pINCY | Library was constructed using RNA isolated from myometrium removed from a 41-year-old Caucasian female during vaginal hysterectomy with a dilatation and curettage and untreated smooth muscle cells removed from the renal vein of a 57-year-old Caucasian male. Pathology indicated the myometrium and cervix were unremarkable. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. Medical history included an unspecified menstrual disorder, ventral hernia, normal delivery, a benign ovarian neoplasm, and tobacco abuse. |

Table 6 (cont.)

| Library | Vector | Library Description |
|-----------|----------|--|
| MYEPTXT02 | pINCY | The library was constructed using RNA isolated from a treated K-562 cell line, derived from chronic myelogenous leukemia precursor cells removed from a 53-year-old female. The cells were treated with 1 micromolar PMA for 96 hours. |
| SINTFEE02 | PCDNA2.1 | This 5' biased random primed library was constructed using RNA isolated from small intestine tissue removed from a Caucasian male fetus who died from Patau's syndrome (trisomy 13) at 20-weeks' gestation. Serology was negative. |
| SINTNOR01 | PCDNA2.1 | This random primed library was constructed using RNA isolated from small intestine tissue removed from a 31-year-old Caucasian female during Roux-en-Y gastric bypass. Patient history included clinical obesity. |
| THYMNOR02 | pINCY | The library was constructed using RNA isolated from thymus tissue removed from a 2-year-old Caucasian female during a thymectomy and patch closure of left atrioventricular fistula. Pathology indicated there was no gross abnormality of the thymus. The patient presented with congenital heart abnormalities. Patient history included double inlet left ventricle and a rudimentary right ventricle, pulmonary hypertension, cyanosis, subaortic stenosis, seizures, and a fracture of the skull base. Family history included reflux neuropathy. |
| TLYMTXT02 | pINCY | Library was constructed using RNA isolated from CD4+ T cells obtained from a pool of donors. The cells were treated with CD3 antibodies. |
| TONGTUT01 | PSPORT1 | Library was constructed using RNA isolated from tongue tumor tissue obtained from a 36-year-old Caucasian male during a hemiglossectomy. Pathology indicated recurrent invasive grade 2 squamous-cell carcinoma. |
| UTRSNOT12 | pINCY | Library was constructed using RNA isolated from uterine myometrial tissue removed from a 41-year-old Caucasian female during a vaginal hysterectomy with dilation and curettage. The endometrium was secretory and contained fragments of endometrial polyps. Benign endo- and ectocervical mucosa were identified in the endocervix. Pathology for the associated tumor tissue indicated uterine leiomyoma. Patient history included ventral hernia and a benign ovarian neoplasm. |

Table 7

| Program | Description | Reference | Parameter Threshold |
|-------------------|---|--|---|
| ABI FACTURA | A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences. | Applied Biosystems, Foster City, CA. | |
| ABI/PARACEL FDF | A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences. | Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA. | Mismatch <50% |
| ABI AutoAssembler | A program that assembles nucleic acid sequences. | Applied Biosystems, Foster City, CA. | |
| BLAST | A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx. | Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25:3389-3402. | ESTs: Probability value= 1.0E-8 or less Full Length sequences: Probability value= 1.0E-10 or less |
| FASTA | A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises at least five functions: fasta, tfasta, fastx, tfastx, and ssearch. | Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad. Sci. USA 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183:63-98; and Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489. | ESTs: fasta E value=1.06E-6 Assembled ESTs: fasta Identity= 95% or greater and Match length=200 bases or greater; fastx E value= 1.0E-8 or less Full Length sequences: fastx score= 100 or greater |
| BLOCKS | A BLOCKS IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions. | Henikoff, S. and J.G. Henikoff (1991) Nucleic Acids Res. 19:6565-6572; Henikoff, J.G. and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Artwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37:417-424. | Probability value= 1.0E-3 or less |
| HMMER | An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM. | Krogh, A. et al. (1994) J. Mol. Biol. 235:1501-1531; Sonnhammer, E.L.L. et al. (1998) Nucleic Acids Res. 26:320-322; Durbin, R. et al. (1998) Our World View, in a Nutshell, Cambridge Univ. Press, pp. 1-350. | PFAM hits: Probability value= 1.0E-3 or less Signal peptide hits: Score= 0 or greater |

Table 7 (cont.)

| Program | Description | Reference | Parameter Threshold |
|-------------|---|--|---|
| ProfileScan | An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite. | Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, M. et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221. | Normalized quality score > GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1. |
| Phred | A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability. | Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194. | |
| Phrap | A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences. | Smith, T.F. and M.S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M.S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA. | Score= 120 or greater; Match length= 56 or greater |
| Consed | A graphical tool for viewing and editing Phrap assemblies. | Gordon, D. et al. (1998) Genome Res. 8:195-202. | |
| SPScan | A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides. | Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12:431-439. | Score=3.5 or greater |
| TMAP | A program that uses weight matrices to delineate transmembrane segments on protein sequences and determine orientation. | Persson, B. and P. Argos (1994) J. Mol. Biol. 237:182-192; Persson, B. and P. Argos (1996) Protein Sci. 5:363-371. | |
| TMHMMER | A program that uses a hidden Markov model (HMM) to delineate transmembrane segments on protein sequences and determine orientation. | Sonnhammer, E.L. et al. (1998) Proc. Sixth Intl. Conf. on Intelligent Systems for Mol. Biol., Glasgow et al., eds., The Am. Assoc. for Artificial Intelligence Press, Menlo Park, CA, pp. 175-182. | |
| Motifs | A program that searches amino acid sequences for patterns that matched those defined in Prosite. | Bairoch, A. et al. (1997) Nucleic Acids Res. 25:217-221; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI. | |

What is claimed is:

1. An isolated polypeptide selected from the group consisting of:
 - a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-24,
 - b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-24,
 - c) a biologically active fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, and
 - d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.
2. An isolated polypeptide of claim 1 selected from the group consisting of SEQ ID NO:1-24.
3. An isolated polynucleotide encoding a polypeptide of claim 1.
4. An isolated polynucleotide encoding a polypeptide of claim 2.
5. An isolated polynucleotide of claim 4 selected from the group consisting of SEQ ID NO:25-48.
6. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.
7. A cell transformed with a recombinant polynucleotide of claim 6.
8. A transgenic organism comprising a recombinant polynucleotide of claim 6.
9. A method of producing a polypeptide of claim 1, the method comprising:
 - a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

- b) recovering the polypeptide so expressed.

10. A method of claim 9, wherein the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.

5

11. An isolated antibody which specifically binds to a polypeptide of claim 1.

12. An isolated polynucleotide selected from the group consisting of:

- 10 a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48,
b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:25-48,
c) a polynucleotide complementary to a polynucleotide of a),
15 d) a polynucleotide complementary to a polynucleotide of b), and
e) an RNA equivalent of a)-d).

13. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 12.

20

14. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 12, the method comprising:

- 25 a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide or fragments thereof, and
b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

30

15. A method of claim 14, wherein the probe comprises at least 60 contiguous nucleotides.

16. A method of detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 12, the method comprising:

- a) amplifying said target polynucleotide or fragment thereof using polymerase chain reaction amplification, and
- b) detecting the presence or absence of said amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

5

17. A composition comprising a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

18. A composition of claim 17, wherein the polypeptide has an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.

19. A method for treating a disease or condition associated with decreased expression of functional PKIN, comprising administering to a patient in need of such treatment the composition of claim 17.

15

20. A method of screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting agonist activity in the sample.

20

21. A composition comprising an agonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

22. A method for treating a disease or condition associated with decreased expression of functional PKIN, comprising administering to a patient in need of such treatment a composition of claim 21.

23. A method of screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

- a) exposing a sample comprising a polypeptide of claim 1 to a compound, and
- b) detecting antagonist activity in the sample.

30

24. A composition comprising an antagonist compound identified by a method of claim 23 and a pharmaceutically acceptable excipient.

25. A method for treating a disease or condition associated with overexpression of functional PKIN, comprising administering to a patient in need of such treatment a composition of claim 24.

26. A method of screening for a compound that specifically binds to the polypeptide of claim 1, the method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under suitable conditions, and
- b) detecting binding of the polypeptide of claim 1 to the test compound, thereby identifying a compound that specifically binds to the polypeptide of claim 1.

10

27. A method of screening for a compound that modulates the activity of the polypeptide of claim 1, the method comprising:

- a) combining the polypeptide of claim 1 with at least one test compound under conditions permissive for the activity of the polypeptide of claim 1,
- 15 b) assessing the activity of the polypeptide of claim 1 in the presence of the test compound, and
- c) comparing the activity of the polypeptide of claim 1 in the presence of the test compound with the activity of the polypeptide of claim 1 in the absence of the test compound, wherein a change in the activity of the polypeptide of claim 1 in the presence of the test compound is indicative of a compound that modulates the activity
- 20 of the polypeptide of claim 1.

20

28. A method of screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 5, the method comprising:

25

- a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,
- b) detecting altered expression of the target polynucleotide, and
- c) comparing the expression of the target polynucleotide in the presence of varying
- 30 amounts of the compound and in the absence of the compound.

30

29. A method of assessing toxicity of a test compound, the method comprising:

- a) treating a biological sample containing nucleic acids with the test compound,

- b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 12 under conditions whereby a specific hybridization complex is formed between said probe and a target polynucleotide in the biological sample, said target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 12 or fragment thereof,
- 5 c) quantifying the amount of hybridization complex, and
- d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample is
- 10 indicative of toxicity of the test compound.

30. A diagnostic test for a condition or disease associated with the expression of PKIN in a biological sample, the method comprising:

- a) combining the biological sample with an antibody of claim 11, under conditions suitable for the antibody to bind the polypeptide and form an antibody:polypeptide complex,
- 15 and
- b) detecting the complex, wherein the presence of the complex correlates with the presence of the polypeptide in the biological sample.

20 31. The antibody of claim 11, wherein the antibody is:

- a) a chimeric antibody,
- b) a single chain antibody,
- c) a Fab fragment,
- d) a F(ab')₂ fragment, or
- 25 e) a humanized antibody.

32. A composition comprising an antibody of claim 11 and an acceptable excipient.

33. A method of diagnosing a condition or disease associated with the expression of PKIN in a subject, comprising administering to said subject an effective amount of the composition of claim 32.

30

34. A composition of claim 32, wherein the antibody is labeled.

35. A method of diagnosing a condition or disease associated with the expression of PKIN in a subject, comprising administering to said subject an effective amount of the composition of claim 34.

36. A method of preparing a polyclonal antibody with the specificity of the antibody of claim 11, the method comprising:

- a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibodies from said animal, and
- 10 c) screening the isolated antibodies with the polypeptide, thereby identifying a polyclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.

37. A polyclonal antibody produced by a method of claim 36.

15

38. A composition comprising the polyclonal antibody of claim 37 and a suitable carrier.

39. A method of making a monoclonal antibody with the specificity of the antibody of claim 11, the method comprising:

- 20 a) immunizing an animal with a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24, or an immunogenic fragment thereof, under conditions to elicit an antibody response,
- b) isolating antibody producing cells from the animal,
- c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells,
- 25 d) culturing the hybridoma cells, and
- e) isolating from the culture monoclonal antibody which binds specifically to a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.

30

40. A monoclonal antibody produced by a method of claim 39.

41. A composition comprising the monoclonal antibody of claim 40 and a suitable carrier.

42. The antibody of claim 11, wherein the antibody is produced by screening a Fab expression library.

43. The antibody of claim 11, wherein the antibody is produced by screening a recombinant immunoglobulin library.

44. A method of detecting a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24 in a sample, the method comprising:

- a) incubating the antibody of claim 11 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) detecting specific binding, wherein specific binding indicates the presence of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24 in the sample.

45. A method of purifying a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24 from a sample, the method comprising:

- a) incubating the antibody of claim 11 with a sample under conditions to allow specific binding of the antibody and the polypeptide, and
- b) separating the antibody from the sample and obtaining the purified polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-24.

46. A microarray wherein at least one element of the microarray is a polynucleotide of claim 13.

47. A method of generating a transcript image of a sample which contains polynucleotides, the method comprising:

- a) labeling the polynucleotides of the sample,
- b) contacting the elements of the microarray of claim 46 with the labeled polynucleotides of the sample under conditions suitable for the formation of a hybridization complex, and
- c) quantifying the expression of the polynucleotides in the sample.

48. An array comprising different nucleotide molecules affixed in distinct physical locations on a solid substrate, wherein at least one of said nucleotide molecules comprises a first oligonucleotide

or polynucleotide sequence specifically hybridizable with at least 30 contiguous nucleotides of a target polynucleotide, and wherein said target polynucleotide is a polynucleotide of claim 12.

49. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is
5 completely complementary to at least 30 contiguous nucleotides of said target polynucleotide.

50. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to at least 60 contiguous nucleotides of said target polynucleotide.

10 51. An array of claim 48, wherein said first oligonucleotide or polynucleotide sequence is completely complementary to said target polynucleotide.

52. An array of claim 48, which is a microarray.

15 53. An array of claim 48, further comprising said target polynucleotide hybridized to a nucleotide molecule comprising said first oligonucleotide or polynucleotide sequence.

54. An array of claim 48, wherein a linker joins at least one of said nucleotide molecules to said solid substrate.

20 55. An array of claim 48, wherein each distinct physical location on the substrate contains multiple nucleotide molecules, and the multiple nucleotide molecules at any single distinct physical location have the same sequence, and each distinct physical location on the substrate contains nucleotide molecules having a sequence which differs from the sequence of nucleotide molecules at
25 another distinct physical location on the substrate.

56. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

57. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:2.

30 58. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:3.

59. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:4.

60. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:5.

61. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:6.

5 62. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:7.

63. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:8.

64. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:9.

10

65. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:10.

66. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:11.

15

67. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:12.

68. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:13.

69. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:14.

20

70. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:15.

71. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:16.

25

72. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:17.

73. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:18.

74. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:19.

30

75. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:20.

76. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:21.

77. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:22.

78. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:23.

5 79. A polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:24.

80. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:25.

81. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:26.

10 82. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:27.

83. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:28.

15 84. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:29.

85. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:30.

86. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:31.

20 87. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:32.

88. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:33.

25 89. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:34.

90. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:35.

91. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:36.

30 92. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:37.

93. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:38.

94. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:39.
95. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:40.
- 5 96. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:41.
97. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:42.
98. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:43.
- 10 99. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID NO:44.
100. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID
NO:45.
- 15 101. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID
NO:46.
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20 NO:47.
103. A polynucleotide of claim 12, comprising the polynucleotide sequence of SEQ ID
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WALIA, Narinder K.
HAFALIA, April J.A.
YAO, Monique G.
GANDHI, Ameena R.
GURURAJAN, Rajagopal
DING, Li
PATTERSON, Chandra
YUE, Henry
BAUGHN, Mariah R.
TRIBOULEY, Catherine M.
THORNTON, Michael
ELLIOTT, Vicki S.
LU, Yan
ISON, Craig H.
AU-YOUNG, Janice
TANG, Y. Tom
AZIMZAI, Yalda
BURRILL, John D.
MARCUS, Gregory A.
ZINGLER, Kurt A.
LU, Dyung Aina M.
LAL, Preeti G.
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| Asp | Gly | Pro | Ala | Gln | Thr | Asn | Gly | Gln | Cys | Phe | Ser | Val | Glu | Thr |
| | | | | 20 | | | | | 25 | | | | | 30 |
| Leu | Leu | Asp | Ile | Leu | Ile | Cys | Leu | Tyr | Asp | Glu | Cys | Asn | Asn | Ser |
| | | | | 35 | | | | | 40 | | | | | 45 |
| Pro | Leu | Arg | Arg | Glu | Lys | Asn | Ile | Leu | Glu | Tyr | Leu | Glu | Trp | Ala |
| | | | | 50 | | | | | 55 | | | | | 60 |
| Lys | Pro | Phe | Thr | Ser | Lys | Val | Lys | Gln | Met | Arg | Leu | His | Arg | Glu |
| | | | | 65 | | | | | 70 | | | | | 75 |
| Asp | Phe | Glu | Ile | Leu | Lys | Val | Ile | Gly | Arg | Gly | Ala | Phe | Gly | Glu |
| | | | | 80 | | | | | 85 | | | | | 90 |
| Val | Ala | Val | Val | Lys | Leu | Lys | Asn | Ala | Asp | Lys | Val | Phe | Ala | Met |
| | | | | 95 | | | | | 100 | | | | | 105 |
| Lys | Ile | Leu | Asn | Lys | Trp | Glu | Met | Leu | Lys | Arg | Ala | Glu | Thr | Ala |
| | | | | 110 | | | | | 115 | | | | | 120 |
| Cys | Phe | Arg | Glu | Glu | Arg | Asp | Val | Leu | Val | Asn | Gly | Asp | Asn | Lys |
| | | | | 125 | | | | | 130 | | | | | 135 |
| Trp | Ile | Thr | Thr | Leu | His | Tyr | Ala | Phe | Gln | Asp | Asp | Asn | Asn | Leu |
| | | | | 140 | | | | | 145 | | | | | 150 |
| Tyr | Leu | Val | Met | Asp | Tyr | Tyr | Val | Gly | Gly | Asp | Leu | Leu | Thr | Leu |
| | | | | 155 | | | | | 160 | | | | | 165 |
| Leu | Ser | Lys | Phe | Glu | Asp | Arg | Leu | Pro | Glu | Asp | Met | Ala | Arg | Phe |
| | | | | 170 | | | | | 175 | | | | | 180 |
| Tyr | Leu | Ala | Glu | Met | Val | Ile | Ala | Ile | Asp | Ser | Val | His | Gln | Leu |
| | | | | 185 | | | | | 190 | | | | | 195 |
| His | Tyr | Val | His | Arg | Asp | Ile | Lys | Pro | Asp | Asn | Ile | Leu | Met | Asp |
| | | | | 200 | | | | | 205 | | | | | 210 |
| Met | Asn | Gly | His | Ile | Arg | Leu | Ala | Asp | Phe | Gly | Ser | Cys | Leu | Lys |
| | | | | 215 | | | | | 220 | | | | | 225 |
| Leu | Met | Glu | Asp | Gly | Thr | Val | Gln | Ser | Ser | Val | Ala | Val | Gly | Thr |
| | | | | 230 | | | | | 235 | | | | | 240 |
| Pro | Asp | Tyr | Ile | Ser | Pro | Glu | Ile | Leu | Gln | Ala | Met | Glu | Asp | Gly |
| | | | | 245 | | | | | 250 | | | | | 255 |
| Lys | Gly | Arg | Tyr | Gly | Pro | Glu | Cys | Asp | Trp | Trp | Ser | Leu | Gly | Val |
| | | | | 260 | | | | | 265 | | | | | 270 |
| Cys | Met | Tyr | Glu | Met | Leu | Tyr | Gly | Glu | Thr | Pro | Phe | Tyr | Ala | Glu |
| | | | | 275 | | | | | 280 | | | | | 285 |
| Ser | Leu | Val | Glu | Thr | Tyr | Gly | Lys | Ile | Met | Asn | His | Lys | Glu | Arg |
| | | | | 290 | | | | | 295 | | | | | 300 |
| Phe | Gln | Phe | Pro | Ala | Gln | Val | Thr | Asp | Val | Ser | Glu | Asn | Ala | Lys |
| | | | | 305 | | | | | 310 | | | | | 315 |

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Leu | Ile | Arg | Arg | Leu | Ile | Cys | Ser | Arg | Glu | His | Arg | Leu | Gly |
| | | | | 320 | | | | | 325 | | | | | 330 |
| Gln | Asn | Gly | Ile | Glu | Asp | Phe | Lys | Lys | His | Pro | Phe | Phe | Ser | Gly |
| | | | | 335 | | | | | 340 | | | | | 345 |
| Ile | Asp | Trp | Asp | Asn | Ile | Arg | Asn | Cys | Glu | Ala | Pro | Tyr | Ile | Pro |
| | | | | 350 | | | | | 355 | | | | | 360 |
| Glu | Val | Ser | Ser | Pro | Thr | Asp | Thr | Ser | Asn | Phe | Asp | Val | Asp | Asp |
| | | | | 365 | | | | | 370 | | | | | 375 |
| Asp | Cys | Leu | Lys | Asn | Ser | Glu | Thr | Met | Pro | Pro | Pro | Thr | His | Thr |
| | | | | 380 | | | | | 385 | | | | | 390 |
| Ala | Phe | Ser | Gly | His | His | Leu | Pro | Phe | Val | Gly | Phe | Thr | Tyr | Thr |
| | | | | 395 | | | | | 400 | | | | | 405 |
| Ser | Ser | Cys | Val | Leu | Ser | Asp | Arg | Ser | Cys | Leu | Arg | Val | Thr | Ala |
| | | | | 410 | | | | | 415 | | | | | 420 |
| Gly | Pro | Thr | Ser | Leu | Asp | Leu | Asp | Val | Asn | Val | Gln | Arg | Thr | Leu |
| | | | | 425 | | | | | 430 | | | | | 435 |
| Asp | Asn | Asn | Leu | Ala | Thr | Glu | Ala | Tyr | Glu | Arg | Arg | Ile | Lys | Arg |
| | | | | 440 | | | | | 445 | | | | | 450 |
| Leu | Glu | Gln | Glu | Lys | Leu | Glu | Leu | Ser | Arg | Lys | Leu | Gln | Glu | Ser |
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| Thr | Gln | Thr | Val | Gln | Ala | Leu | Gln | Tyr | Ser | Thr | Val | Asp | Gly | Pro |
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| Leu | Thr | Ala | Ser | Lys | Asp | Leu | Glu | Ile | Lys | Asn | Leu | Lys | Glu | Glu |
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| Ile | Glu | Lys | Leu | Arg | Lys | Gln | Val | Thr | Glu | Ser | Ser | His | Leu | Glu |
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| Gln | Gln | Leu | Glu | Glu | Ala | Asn | Ala | Val | Arg | Gln | Glu | Leu | Asp | Asp |
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| Ala | Phe | Arg | Gln | Ile | Lys | Ala | Tyr | Glu | Lys | Gln | Ile | Lys | Thr | Leu |
| | | | | 530 | | | | | 535 | | | | | 540 |
| Gln | Gln | Glu | Arg | Glu | Asp | Leu | Asn | Lys | Glu | Leu | Val | Gln | Ala | Ser |
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| Glu | Arg | Leu | Lys | Asn | Gln | Ser | Lys | Glu | Leu | Lys | Asp | Ala | His | Cys |
| | | | | 560 | | | | | 565 | | | | | 570 |
| Gln | Arg | Lys | Leu | Ala | Met | Gln | Glu | Phe | Met | Glu | Ile | Asn | Glu | Arg |
| | | | | 575 | | | | | 580 | | | | | 585 |
| Leu | Thr | Glu | Leu | His | Thr | Gln | Lys | Gln | Lys | Leu | Ala | Arg | His | Val |
| | | | | 590 | | | | | 595 | | | | | 600 |
| Arg | Asp | Lys | Glu | Glu | Glu | Val | Asp | Leu | Val | Met | Gln | Lys | Val | Glu |
| | | | | 605 | | | | | 610 | | | | | 615 |
| Ser | Leu | Arg | Gln | Glu | Leu | Arg | Arg | Thr | Glu | Arg | Ala | Lys | Lys | Glu |
| | | | | 620 | | | | | 625 | | | | | 630 |
| Leu | Glu | Val | His | Thr | Glu | Ala | Leu | Ala | Ala | Glu | Ala | Ser | Lys | Asp |
| | | | | 635 | | | | | 640 | | | | | 645 |
| Arg | Lys | Leu | Arg | Glu | Gln | Ser | Glu | His | Tyr | Ser | Lys | Gln | Leu | Glu |
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| Asn | Glu | Leu | Glu | Gly | Leu | Lys | Gln | Lys | Gln | Ile | Ser | Tyr | Ser | Pro |
| | | | | 665 | | | | | 670 | | | | | 675 |
| Gly | Val | Cys | Ser | Ile | Glu | His | Gln | Gln | Glu | Ile | Thr | Lys | Leu | Lys |
| | | | | 680 | | | | | 685 | | | | | 690 |
| Thr | Asp | Leu | Glu | Lys | Lys | Ser | Ile | Phe | Tyr | Glu | Glu | Glu | Leu | Ser |
| | | | | 695 | | | | | 700 | | | | | 705 |
| Lys | Arg | Glu | Gly | Ile | His | Ala | Asn | Glu | Ile | Lys | Asn | Leu | Lys | Lys |
| | | | | 710 | | | | | 715 | | | | | 720 |
| Glu | Leu | His | Asp | Ser | Glu | Gly | Gln | Gln | Leu | Ala | Leu | Asn | Lys | Glu |
| | | | | 725 | | | | | 730 | | | | | 735 |

| | | | |
|---|------|------|------|
| Ile Met Ile Leu Lys Asp Lys Leu Glu Lys Thr Arg Arg Glu Ser | 740 | 745 | 750 |
| Gln Ser Glu Arg Glu Glu Phe Glu Ser Glu Phe Lys Gln Gln Tyr | 755 | 760 | 765 |
| Glu Arg Glu Lys Val Leu Leu Thr Glu Glu Asn Lys Lys Leu Thr | 770 | 775 | 780 |
| Ser Glu Leu Asp Lys Leu Thr Thr Leu Tyr Glu Asn Leu Ser Ile | 785 | 790 | 795 |
| His Asn Gln Gln Leu Glu Glu Glu Val Lys Asp Leu Ala Asp Lys | 800 | 805 | 810 |
| Lys Glu Ser Val Ala His Trp Glu Ala Gln Ile Thr Glu Ile Ile | 815 | 820 | 825 |
| Gln Trp Val Ser Asp Glu Lys Asp Ala Arg Gly Tyr Leu Gln Ala | 830 | 835 | 840 |
| Leu Ala Ser Lys Met Thr Glu Glu Leu Glu Ala Leu Arg Asn Ser | 845 | 850 | 855 |
| Ser Leu Gly Thr Arg Ala Thr Asp Met Pro Trp Lys Met Arg Arg | 860 | 865 | 870 |
| Phe Ala Lys Leu Asp Met Ser Ala Arg Leu Glu Leu Gln Ser Ala | 875 | 880 | 885 |
| Leu Asp Ala Glu Ile Arg Ala Lys Gln Ala Ile Gln Glu Glu Leu | 890 | 895 | 900 |
| Asn Lys Val Lys Ala Ser Asn Ile Ile Thr Glu Cys Lys Leu Lys | 905 | 910 | 915 |
| Asp Ser Glu Lys Lys Asn Leu Glu Leu Leu Ser Glu Ile Glu Gln | 920 | 925 | 930 |
| Leu Ile Lys Asp Thr Glu Glu Leu Arg Ser Glu Lys Gly Ile Glu | 935 | 940 | 945 |
| His Gln Asp Ser Gln His Ser Phe Leu Ala Phe Leu Asn Thr Pro | 950 | 955 | 960 |
| Thr Asp Ala Leu Asp Gln Phe Glu Thr Val Asp Ser Thr Pro Leu | 965 | 970 | 975 |
| Ser Val His Thr Pro Thr Leu Arg Lys Lys Gly Cys Pro Gly Ser | 980 | 985 | 990 |
| Thr Gly Phe Pro Pro Lys Arg Lys Thr His Gln Phe Phe Val Lys | 995 | 1000 | 1005 |
| Ser Phe Thr Thr Pro Thr Lys Cys His Gln Cys Thr Ser Leu Met | 1010 | 1015 | 1020 |
| Val Gly Leu Ile Arg Gln Gly Cys Ser Cys Glu Val Cys Gly Phe | 1025 | 1030 | 1035 |
| Ser Cys His Ile Thr Cys Val Asn Lys Ala Pro Thr Thr Cys Pro | 1040 | 1045 | 1050 |
| Val Pro Pro Glu Gln Thr Lys Gly Pro Leu Gly Ile Asp Pro Gln | 1055 | 1060 | 1065 |
| Lys Gly Ile Gly Thr Ala Tyr Glu Gly His Val Arg Ile Pro Lys | 1070 | 1075 | 1080 |
| Pro Ala Gly Val Lys Lys Gly Trp Gln Arg Ala Leu Ala Ile Val | 1085 | 1090 | 1095 |
| Cys Asp Phe Lys Leu Phe Leu Tyr Asp Ile Ala Glu Gly Lys Ala | 1100 | 1105 | 1110 |
| Ser Gln Pro Ser Val Val Ile Ser Gln Val Ile Asp Met Arg Asp | 1115 | 1120 | 1125 |
| Glu Glu Phe Ser Val Ser Ser Val Leu Ala Ser Asp Val Ile His | 1130 | 1135 | 1140 |
| Ala Ser Arg Lys Asp Ile Pro Cys Ile Phe Arg Val Thr Ala Ser | 1145 | 1150 | 1155 |

| | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|------|------|
| Gln | Leu | Ser | Ala | Ser | Asn | Asn | Lys | Cys | Ser | Ile | Leu | Met | Leu | Ala | 1160 | 1165 | 1170 |
| Asp | Thr | Glu | Asn | Glu | Lys | Asn | Lys | Trp | Val | Gly | Val | Leu | Ser | Glu | 1175 | 1180 | 1185 |
| Leu | His | Lys | Ile | Leu | Lys | Lys | Asn | Lys | Phe | Arg | Asp | Arg | Ser | Val | 1190 | 1195 | 1200 |
| Tyr | Val | Pro | Lys | Glu | Ala | Tyr | Asp | Ser | Thr | Leu | Pro | Leu | Ile | Lys | 1205 | 1210 | 1215 |
| Thr | Thr | Gln | Ala | Ala | Ala | Ile | Ile | Asp | His | Glu | Arg | Ile | Ala | Leu | 1220 | 1225 | 1230 |
| Gly | Asn | Glu | Glu | Gly | Leu | Phe | Val | Val | His | Val | Thr | Lys | Asp | Glu | 1235 | 1240 | 1245 |
| Ile | Ile | Arg | Val | Gly | Asp | Asn | Lys | Lys | Ile | His | Gln | Ile | Glu | Leu | 1250 | 1255 | 1260 |
| Ile | Pro | Asn | Asp | Gln | Leu | Val | Ala | Val | Ile | Ser | Gly | Arg | Asn | Arg | 1265 | 1270 | 1275 |
| His | Val | Arg | Leu | Phe | Pro | Met | Ser | Ala | Leu | Asp | Gly | Arg | Glu | Thr | 1280 | 1285 | 1290 |
| Asp | Phe | Tyr | Lys | Leu | Ser | Glu | Thr | Lys | Gly | Cys | Gln | Thr | Val | Thr | 1295 | 1300 | 1305 |
| Ser | Gly | Lys | Val | Arg | His | Gly | Ala | Leu | Thr | Cys | Leu | Cys | Val | Ala | 1310 | 1315 | 1320 |
| Met | Lys | Arg | Gln | Val | Leu | Cys | Tyr | Glu | Leu | Phe | Gln | Ser | Lys | Thr | 1325 | 1330 | 1335 |
| Arg | His | Arg | Lys | Phe | Lys | Glu | Ile | Gln | Val | Pro | Tyr | Asn | Val | Gln | 1340 | 1345 | 1350 |
| Trp | Met | Ala | Ile | Phe | Ser | Glu | Gln | Leu | Cys | Val | Gly | Phe | Gln | Ser | 1355 | 1360 | 1365 |
| Gly | Phe | Leu | Arg | Tyr | Pro | Leu | Asn | Gly | Glu | Gly | Asn | Pro | Tyr | Ser | 1370 | 1375 | 1380 |
| Met | Leu | His | Ser | Asn | Asp | His | Thr | Leu | Ser | Phe | Ile | Ala | His | Gln | 1385 | 1390 | 1395 |
| Pro | Met | Asp | Ala | Ile | Cys | Ala | Val | Glu | Ile | Ser | Ser | Lys | Glu | Tyr | 1400 | 1405 | 1410 |
| Leu | Leu | Cys | Phe | Asn | Ser | Ile | Gly | Ile | Tyr | Thr | Asp | Cys | Gln | Gly | 1415 | 1420 | 1425 |
| Arg | Arg | Ser | Arg | Gln | Gln | Glu | Leu | Met | Trp | Pro | Ala | Asn | Pro | Ser | 1430 | 1435 | 1440 |
| Ser | Cys | Cys | Tyr | Asn | Ala | Pro | Tyr | Leu | Ser | Val | Tyr | Ser | Glu | Asn | 1445 | 1450 | 1455 |
| Ala | Val | Asp | Ile | Phe | Asp | Val | Asn | Ser | Met | Glu | Trp | Ile | Gln | Thr | 1460 | 1465 | 1470 |
| Leu | Pro | Leu | Lys | Lys | Val | Arg | Pro | Leu | Asn | Asn | Glu | Gly | Ser | Leu | 1475 | 1480 | 1485 |
| Asn | Leu | Leu | Gly | Leu | Glu | Thr | Ile | Arg | Leu | Ile | Tyr | Phe | Lys | Asn | 1490 | 1495 | 1500 |
| Lys | Met | Ala | Glu | Gly | Asp | Glu | Leu | Val | Val | Pro | Glu | Thr | Ser | Asp | 1505 | 1510 | 1515 |
| Asn | Ser | Arg | Lys | Gln | Met | Val | Arg | Asn | Ile | Asn | Asn | Lys | Arg | Arg | 1520 | 1525 | 1530 |
| Tyr | Ser | Phe | Arg | Val | Pro | Glu | Glu | Glu | Arg | Met | Gln | Gln | Arg | Arg | 1535 | 1540 | 1545 |
| Glu | Met | Leu | Arg | Asp | Pro | Glu | Met | Arg | Asn | Lys | Leu | Ile | Ser | Asn | 1550 | 1555 | 1560 |
| Pro | Thr | Asn | Phe | Asn | His | Ile | Ala | His | Met | Gly | Pro | Gly | Asp | Gly | 1565 | 1570 | 1575 |

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Ile Gln Ile Leu Lys Asp Leu Pro Met Asn Pro Arg Pro Gln Glu
      1580                      1585                      1590
Ser Arg Thr Val Phe Ser Gly Ser Val Ser Ile Pro Ser Ile Thr
      1595                      1600                      1605
Lys Ser Arg Pro Glu Pro Gly Arg Ser Met Ser Ala Ser Ser Gly
      1610                      1615                      1620
Leu Ser Ala Arg Ser Ser Ala Gln Asn Gly Ser Ala Leu Lys Arg
      1625                      1630                      1635
Glu Phe Ser Gly Gly Ser Tyr Ser Ala Lys Arg Gln Pro Met Pro
      1640                      1645                      1650
Ser Pro Ser Glu Gly Ser Leu Ser Ser Gly Gly Met Asp Gln Gly
      1655                      1660                      1665
Ser Asp Ala Pro Ala Arg Asp Phe Asp Gly Glu Asp Ser Asp Ser
      1670                      1675                      1680
Pro Arg His Ser Thr Ala Ser Asn Ser Ser Asn Leu Ser Ser Pro
      1685                      1690                      1695
Pro Ser Pro Val Ser Pro Arg Lys Thr Lys Ser Leu Ser Leu Glu
      1700                      1705                      1710
Ser Thr Asp Arg Gly Ser Trp Asp Pro
      1715

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Ala Glu Ile Arg Gly Gly Ala Glu Arg Gly Glu Phe Pro Tyr Leu
      35      40      45
Gly Arg Leu Arg Glu Glu Pro Gly Gly Gly Thr Cys Tyr Val Val
      50      55      60
Ser Gly Lys Ala Pro Ser Pro Gly Asp Val Leu Leu Glu Val Asn
      65      70      75
Gly Thr Pro Val Ser Gly Leu Thr Asn Arg Asp Thr Leu Ala Val
      80      85      90
Ile Arg His Phe Arg Glu Pro Ile Arg Leu Lys Thr Val Lys Pro
      95     100     105
Gly Lys Val Ile Asn Lys Asp Leu Arg His Tyr Leu Ser Leu Gln
      110     115     120
Phe Gln Lys Gly Ser Ile Asp His Lys Leu Gln Gln Val Ile Arg
      125     130     135
Asp Asn Leu Tyr Leu Arg Thr Ile Pro Cys Thr Thr Arg Ala Pro
      140     145     150
Arg Asp Gly Glu Val Pro Gly Val Asp Tyr Asn Phe Ile Ser Val
      155     160     165
Glu Gln Phe Lys Ala Leu Glu Glu Ser Gly Ala Leu Leu Glu Ser
      170     175     180
Gly Thr Tyr Asp Gly Asn Phe Tyr Gly Thr Pro Lys Pro Pro Ala

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| | | | |
|-----------------|---|-------------------------|-----|
| | 185 | 190 | 195 |
| Glu Pro Ser Pro | Phe Gln Pro Asp Pro | Val Asp Gln Val Leu Phe | |
| | 200 | 205 | 210 |
| Asp Asn Glu Phe | Asp Ala Glu Ser Gln Arg Lys Arg Thr Thr Ser | | |
| | 215 | 220 | 225 |
| Val Ser Lys Met | Glu Arg Met Asp Ser Ser Leu Pro Glu Glu Glu | | |
| | 230 | 235 | 240 |
| Glu Asp Glu Asp | Lys Glu Ala Ile Asn Gly Ser Gly Asn Ala Glu | | |
| | 245 | 250 | 255 |
| Asn Arg Glu Arg | His Ser Glu Ser Ser Asp Trp Met Lys Thr Val | | |
| | 260 | 265 | 270 |
| Pro Ser Tyr Asn | Gln Thr Asn Ser Ser Met Asp Phe Arg Asn Tyr | | |
| | 275 | 280 | 285 |
| Met Met Arg Asp | Glu Thr Leu Glu Pro Leu Pro Lys Asn Trp Glu | | |
| | 290 | 295 | 300 |
| Met Ala Tyr Thr | Asp Thr Gly Met Ile Tyr Phe Ile Asp His Asn | | |
| | 305 | 310 | 315 |
| Thr Lys Thr Thr | Thr Trp Leu Asp Pro Arg Leu Cys Lys Lys Ala | | |
| | 320 | 325 | 330 |
| Lys Ala Pro Glu | Asp Cys Glu Asp Gly Glu Leu Pro Tyr Gly Trp | | |
| | 335 | 340 | 345 |
| Glu Lys Ile Glu | Asp Pro Gln Tyr Gly Thr Tyr Tyr Val Asp His | | |
| | 350 | 355 | 360 |
| Leu Asn Gln Lys | Thr Gln Phe Glu Asn Pro Val Glu Glu Ala Lys | | |
| | 365 | 370 | 375 |
| Arg Lys Lys Gln | Leu Gly Gln Val Glu Ile Gly Ser Ser Lys Pro | | |
| | 380 | 385 | 390 |
| Asp Met Glu Lys | Ser His Phe Thr Arg Asp Pro Ser Gln Leu Lys | | |
| | 395 | 400 | 405 |
| Gly Val Leu Val | Arg Ala Ser Leu Lys Lys Ser Thr Met Gly Phe | | |
| | 410 | 415 | 420 |
| Gly Phe Thr Ile | Ile Gly Gly Asp Arg Pro Asp Glu Phe Leu Gln | | |
| | 425 | 430 | 435 |
| Val Lys Asn Val | Leu Lys Asp Gly Pro Ala Ala Gln Asp Gly Lys | | |
| | 440 | 445 | 450 |
| Ile Ala Pro Gly | Asp Val Ile Val Asp Ile Asn Gly Asn Cys Val | | |
| | 455 | 460 | 465 |
| Leu Gly His Thr | His Ala Asp Val Val Gln Met Phe Gln Leu Val | | |
| | 470 | 475 | 480 |
| Pro Val Asn Gln | Tyr Val Asn Leu Thr Leu Cys Arg Gly Tyr Pro | | |
| | 485 | 490 | 495 |
| Leu Pro Asp Asp | Ser Glu Asp Pro Val Val Asp Ile Val Ala Ala | | |
| | 500 | 505 | 510 |
| Thr Pro Val Ile | Asn Gly Gln Ser Leu Thr Lys Gly Glu Thr Cys | | |
| | 515 | 520 | 525 |
| Met Asn Pro Gln | Asp Phe Lys Pro Gly Ala Met Val Leu Glu Gln | | |
| | 530 | 535 | 540 |
| Asn Gly Lys Ser | Gly His Thr Leu Thr Gly Asp Gly Leu Asn Gly | | |
| | 545 | 550 | 555 |
| Pro Ser Asp Ala | Ser Glu Gln Arg Val Ser Met Ala Ser Ser Gly | | |
| | 560 | 565 | 570 |
| Ser Ser Gln Pro | Glu Leu Val Thr Ile Pro Leu Ile Lys Gly Pro | | |
| | 575 | 580 | 585 |
| Lys Gly Phe Gly | Phe Ala Ile Ala Asp Ser Pro Thr Gly Gln Lys | | |
| | 590 | 595 | 600 |
| Val Lys Met Ile | Leu Asp Ser Gln Trp Cys Gln Gly Leu Gln Lys | | |

| | | | | | |
|-----------------|---------------------|-------------------------|------|--|------|
| | 605 | | 610 | | 615 |
| Gly Asp Ile Ile | Lys Glu Ile Tyr His | Gln Asn Val Gln Asn Leu | | | |
| | 620 | | 625 | | 630 |
| Thr His Leu Gln | Val Val Glu Val Leu | Lys Gln Phe Pro Val Gly | | | |
| | 635 | | 640 | | 645 |
| Ala Asp Val Pro | Leu Leu Ile Leu Arg | Gly Gly Pro Pro Ser Pro | | | |
| | 650 | | 655 | | 660 |
| Thr Lys Thr Ala | Lys Met Lys Thr Asp | Lys Lys Glu Asn Ala Gly | | | |
| | 665 | | 670 | | 675 |
| Ser Leu Glu Ala | Ile Asn Glu Pro Ile | Pro Gln Pro Met Pro Phe | | | |
| | 680 | | 685 | | 690 |
| Pro Pro Ser Ile | Ile Arg Ser Gly Ser | Pro Lys Leu Asp Pro Ser | | | |
| | 695 | | 700 | | 705 |
| Glu Val Tyr Leu | Lys Ser Lys Thr Leu | Tyr Glu Asp Lys Pro Pro | | | |
| | 710 | | 715 | | 720 |
| Asn Thr Lys Asp | Leu Asp Val Phe Leu | Arg Lys Gln Glu Ser Gly | | | |
| | 725 | | 730 | | 735 |
| Phe Gly Phe Arg | Val Leu Gly Gly Asp | Gly Pro Asp Gln Ser Ile | | | |
| | 740 | | 745 | | 750 |
| Tyr Ile Gly Ala | Ile Ile Pro Leu Gly | Ala Ala Glu Lys Asp Gly | | | |
| | 755 | | 760 | | 765 |
| Arg Leu Arg Ala | Ala Asp Glu Leu Met | Cys Ile Asp Gly Ile Pro | | | |
| | 770 | | 775 | | 780 |
| Val Lys Gly Lys | Ser His Lys Gln Val | Leu Asp Leu Met Thr Thr | | | |
| | 785 | | 790 | | 795 |
| Ala Ala Arg Asn | Gly His Val Leu Leu | Thr Val Arg Arg Lys Ile | | | |
| | 800 | | 805 | | 810 |
| Phe Tyr Gly Glu | Lys Gln Pro Glu Asp | Asp Ser Ser Gln Ala Phe | | | |
| | 815 | | 820 | | 825 |
| Ile Ser Thr Gln | Asn Gly Ser Pro Arg | Leu Asn Arg Ala Glu Val | | | |
| | 830 | | 835 | | 840 |
| Pro Ala Arg Pro | Ala Pro Gln Glu Pro | Tyr Asp Val Val Leu Gln | | | |
| | 845 | | 850 | | 855 |
| Arg Lys Glu Asn | Glu Gly Phe Gly Phe | Val Ile Leu Thr Ser Lys | | | |
| | 860 | | 865 | | 870 |
| Asn Lys Pro Pro | Pro Gly Val Ile Pro | His Lys Ile Gly Arg Val | | | |
| | 875 | | 880 | | 885 |
| Ile Glu Gly Ser | Pro Ala Asp Arg Cys | Gly Lys Leu Lys Val Gly | | | |
| | 890 | | 895 | | 900 |
| Asp His Ile Ser | Ala Val Asn Gly Gln | Ser Ile Val Glu Leu Ser | | | |
| | 905 | | 910 | | 915 |
| His Asp Asn Ile | Val Gln Leu Ile Lys | Asp Ala Gly Val Thr Val | | | |
| | 920 | | 925 | | 930 |
| Thr Leu Thr Val | Ile Ala Glu Glu Glu | His His Gly Pro Pro Ser | | | |
| | 935 | | 940 | | 945 |
| Gly Thr Asn Ser | Ala Arg Gln Ser Pro | Ala Leu Gln His Arg Pro | | | |
| | 950 | | 955 | | 960 |
| Met Gly Gln Ser | Gln Ala Asn His Ile | Pro Gly Asp Arg Ser Ala | | | |
| | 965 | | 970 | | 975 |
| Leu Glu Gly Glu | Ile Gly Lys Asp Val | Ser Thr Ser Tyr Arg His | | | |
| | 980 | | 985 | | 990 |
| Ser Trp Ser Asp | His Lys His Leu Ala | Gln Pro Asp Thr Ala Val | | | |
| | 995 | | 1000 | | 1005 |
| Ile Ser Val Val | Gly Ser Arg His Asn | Gln Asn Leu Gly Cys Tyr | | | |
| | 1010 | | 1015 | | 1020 |
| Pro Val Glu Leu | Glu Arg Gly Pro Arg | Gly Phe Gly Phe Ser Leu | | | |

| | | |
|---|------|------|
| 1025 | 1030 | 1035 |
| Arg Gly Gly Lys Glu Tyr Asn Met Gly Leu Phe Ile Leu Arg Leu | | |
| 1040 | 1045 | 1050 |
| Ala Glu Asp Gly Pro Ala Ile Lys Asp Gly Arg Ile His Val Gly | | |
| 1055 | 1060 | 1065 |
| Asp Gln Ile Val Glu Ile Asn Gly Glu Pro Thr Gln Gly Ile Thr | | |
| 1070 | 1075 | 1080 |
| His Thr Arg Ala Ile Glu Leu Ile Gln Ala Gly Gly Asn Lys Val | | |
| 1085 | 1090 | 1095 |
| Leu Leu Leu Leu Arg Pro Gly Thr Gly Leu Ile Pro Asp His Gly | | |
| 1100 | 1105 | 1110 |
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| Arg Arg Gln Leu Gly Gln Gly Ala Tyr Gly Ile Val Trp Lys Ala | | |
| 20 | 25 | 30 |
| Val Asp Arg Arg Thr Gly Glu Val Val Ala Ile Lys Lys Ile Phe | | |
| 35 | 40 | 45 |
| Asp Ala Phe Arg Asp Lys Thr Asp Ala Gln Arg Thr Phe Arg Glu | | |
| 50 | 55 | 60 |
| Ile Thr Leu Leu Gln Glu Phe Gly Asp His Pro Asn Ile Ile Ser | | |
| 65 | 70 | 75 |
| Leu Leu Asp Val Ile Arg Ala Glu Asn Asp Arg Asp Ile Tyr Leu | | |
| 80 | 85 | 90 |
| Val Phe Glu Phe Met Asp Thr Asp Leu Asn Ala Val Ile Arg Lys | | |
| 95 | 100 | 105 |
| Gly Gly Leu Leu Gln Asp Val His Val Arg Ser Ile Phe Tyr Gln | | |
| 110 | 115 | 120 |
| Leu Leu Arg Ala Thr Arg Phe Leu His Ser Gly His Val Val His | | |
| 125 | 130 | 135 |
| Arg Asp Gln Lys Pro Ser Asn Val Leu Leu Asp Ala Asn Cys Thr | | |
| 140 | 145 | 150 |
| Val Lys Leu Cys Asp Phe Gly Leu Ala Arg Ser Leu Gly Asp Leu | | |
| 155 | 160 | 165 |
| Pro Glu Gly Pro Glu Asp Gln Ala Val Thr Glu Tyr Val Ala Thr | | |
| 170 | 175 | 180 |
| Arg Trp Tyr Arg Ala Pro Glu Val Leu Leu Ser Ser His Arg Tyr | | |
| 185 | 190 | 195 |
| Thr Leu Gly Val Asp Met Trp Ser Leu Gly Cys Ile Leu Gly Glu | | |
| 200 | 205 | 210 |
| Met Leu Arg Gly Arg Pro Leu Phe Pro Gly Thr Ser Thr Leu His | | |
| 215 | 220 | 225 |
| Gln Leu Glu Leu Ile Leu Glu Thr Ile Pro Pro Pro Ser Glu Glu | | |

| | | |
|---|-----|-----|
| 230 | 235 | 240 |
| Asp Leu Leu Ala Leu Gly Ser Gly Cys Arg Ala Ser Val Leu His | | |
| 245 | 250 | 255 |
| Gln Leu Gly Ser Arg Pro Arg Gln Thr Leu Asp Ala Leu Leu Pro | | |
| 260 | 265 | 270 |
| Pro Asp Thr Ser Pro Glu Ala Leu Asp Leu Leu Arg Arg Leu Leu | | |
| 275 | 280 | 285 |
| Val Phe Ala Pro Asp Lys Arg Leu Ser Ala Thr Gln Met Ile Leu | | |
| 290 | 295 | 300 |
| Glu Cys Gly Gly Ser Ser Gly Thr Ser Arg Glu Lys Gly Pro Glu | | |
| 305 | 310 | 315 |
| Gly Val Ser Pro Ser Gln Ala His Leu His Lys Pro Arg Ala Asp | | |
| 320 | 325 | 330 |
| Pro Gln Leu Pro Ser Arg Thr Pro Val Gln Gly Pro Arg Pro Arg | | |
| 335 | 340 | 345 |
| Pro Gln Ser Ser Pro Gly His Asp Pro Ala Glu His Glu Ser Pro | | |
| 350 | 355 | 360 |
| Arg Ala Ala Lys Asn Val Pro Arg Gln Asn Ser Ala Pro Leu Leu | | |
| 365 | 370 | 375 |
| Gln Thr Ala Leu Leu Gly Asn Gly Glu Arg Pro Pro Gly Ala Lys | | |
| 380 | 385 | 390 |
| Glu Ala Pro Pro Leu Thr Leu Ser Leu Val Lys Pro Ser Gly Arg | | |
| 395 | 400 | 405 |
| Gly Ala Ala Pro Ser Leu Thr Ser Gln Ala Ala Ala Gln Val Ala | | |
| 410 | 415 | 420 |
| Asn Gln Ala Leu Ile Arg Gly Asp Trp Asn Arg Gly Gly Gly Val | | |
| 425 | 430 | 435 |
| Arg Val Ala Ser Val Gln Gln Val Pro Pro Arg Leu Pro Pro Glu | | |
| 440 | 445 | 450 |
| Ala Arg Pro Gly Arg Arg Met Phe Ser Thr Ser Ala Leu Gln Gly | | |
| 455 | 460 | 465 |
| Ala Gln Gly Gly Ala Arg Ala Leu Leu Gly Gly Tyr Ser Gln Ala | | |
| 470 | 475 | 480 |
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| Glu Gly His His Val | | |
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| Tyr His Ser Leu Met Asp Glu Tyr Gly Tyr Glu Val Gly Lys Ala | | |
| 20 | 25 | 30 |
| Ile Gly His Gly Ser Tyr Gly Ser Val Tyr Glu Ala Phe Tyr Thr | | |
| 35 | 40 | 45 |
| Lys Gln Lys Val Met Val Ala Val Lys Ile Ile Ser Lys Lys Lys | | |
| 50 | 55 | 60 |

| | | | | | |
|-----------------|---------------------|---------------------|-----|--|-----|
| | 65 | | 70 | | 75 |
| Phe Gly Arg Arg | Gly Asn Leu His Phe | Ile Arg Phe Pro Thr | Gln | | |
| | 80 | | 85 | | 90 |
| Asp Leu Pro Thr | Phe Ile Gln Met Gly | Arg Asp Lys Asn Phe | Ser | | |
| | 95 | | 100 | | 105 |
| Thr Leu Gln Thr | Val Leu Cys Ala Thr | Gly Gly Gly Ala Tyr | Lys | | |
| | 110 | | 115 | | 120 |
| Phe Glu Lys Asp | Phe Arg Thr Ile Gly | Asn Leu His Leu His | Lys | | |
| | 125 | | 130 | | 135 |
| Leu Asp Glu Leu | Asp Cys Leu Val Lys | Gly Leu Leu Tyr Ile | Asp | | |
| | 140 | | 145 | | 150 |
| Ser Val Ser Phe | Asn Gly Gln Ala Glu | Cys Tyr Tyr Phe Ala | Asn | | |
| | 155 | | 160 | | 165 |
| Ala Ser Glu Pro | Glu Arg Cys Gln Lys | Met Pro Phe Asn Leu | Asp | | |
| | 170 | | 175 | | 180 |
| Asp Pro Tyr Pro | Leu Leu Val Val Asn | Ile Gly Ser Gly Val | Ser | | |
| | 185 | | 190 | | 195 |
| Ile Leu Ala Val | His Ser Lys Asp Asn | Tyr Lys Arg Val Thr | Gly | | |
| | 200 | | 205 | | 210 |
| Thr Ser Leu Gly | Gly Gly Thr Tyr Thr | Gly Phe Met Gln Leu | Leu | | |
| | 215 | | 220 | | 225 |
| Thr Gly Cys Glu | Ser Phe Glu Glu Ala | Leu Glu Met Ala Ser | Lys | | |
| | 230 | | 235 | | 240 |
| Gly Asp Ser Thr | Gln Ala Asp Lys Leu | Val Arg Asp Ile Tyr | Gly | | |
| | 245 | | 250 | | 255 |
| Gly Asp Tyr Glu | Arg Phe Gly Leu Pro | Gly Trp Ala Val Ala | Ser | | |
| | 260 | | 265 | | 270 |
| Ser Phe Gly Asn | Met Ile Tyr Lys Glu | Lys Arg Glu Ser Val | Ser | | |
| | 275 | | 280 | | 285 |
| Lys Glu Asp Leu | Ala Arg Ala Thr Leu | Val Thr Ile Thr Asn | Asn | | |
| | 290 | | 295 | | 300 |
| Ile Gly Ser Val | Ala Arg Met Cys Ala | Val Asn Glu Lys Ile | Asn | | |
| | 305 | | 310 | | 315 |
| Arg Val Val Phe | Val Gly Asn Phe Leu | Arg Val Asn Thr Leu | Ser | | |
| | 320 | | 325 | | 330 |
| Met Lys Leu Leu | Ala Tyr Ala Leu Asp | Tyr Trp Ser Lys Gly | Gln | | |
| | 335 | | 340 | | 345 |
| Leu Lys Ala Leu | Phe Leu Glu His Glu | Gly Tyr Phe Gly Ala | Val | | |
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| Gly Ala Leu Leu | Gly Leu Pro Asn Phe | Ser | | | |
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| Gly Thr Gly Gly | Ala Gly Pro Ala Gly | Arg Leu Leu Pro Pro | Pro |
| 20 | 25 | 30 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Ala | Pro | Gly | Ser | Pro | Ala | Ala | Pro | Ala | Ala | Val | Ser | Pro | Ala | Ala | |
| | | | | 35 | | | | | 40 | | | | | 45 | |
| Gly | Gln | Pro | Arg | Pro | Pro | Ala | Pro | Ala | Ser | Arg | Gly | Pro | Met | Pro | |
| | | | | 50 | | | | | 55 | | | | | 60 | |
| Ala | Arg | Ile | Gly | Tyr | Tyr | Glu | Ile | Asp | Arg | Thr | Ile | Gly | Lys | Gly | |
| | | | | 65 | | | | | 70 | | | | | 75 | |
| Asn | Phe | Ala | Val | Val | Lys | Arg | Ala | Thr | His | Leu | Val | Thr | Lys | Ala | |
| | | | | 80 | | | | | 85 | | | | | 90 | |
| Lys | Val | Ala | Ile | Lys | Ile | Ile | Asp | Lys | Thr | Gln | Leu | Asp | Glu | Glu | |
| | | | | 95 | | | | | 100 | | | | | 105 | |
| Asn | Leu | Lys | Lys | Ile | Phe | Arg | Glu | Val | Gln | Ile | Met | Lys | Met | Leu | |
| | | | | 110 | | | | | 115 | | | | | 120 | |
| Cys | His | Pro | His | Ile | Ile | Arg | Leu | Tyr | Gln | Val | Met | Glu | Thr | Glu | |
| | | | | 125 | | | | | 130 | | | | | 135 | |
| Arg | Met | Ile | Tyr | Leu | Val | Thr | Glu | Tyr | Ala | Ser | Gly | Gly | Glu | Ile | |
| | | | | 140 | | | | | 145 | | | | | 150 | |
| Phe | Asp | His | Leu | Val | Ala | His | Gly | Arg | Met | Ala | Glu | Lys | Glu | Ala | |
| | | | | 155 | | | | | 160 | | | | | 165 | |
| Arg | Arg | Lys | Phe | Lys | Gln | Ile | Val | Thr | Ala | Val | Tyr | Phe | Cys | His | |
| | | | | 170 | | | | | 175 | | | | | 180 | |
| Cys | Arg | Asn | Ile | Val | His | Arg | Asp | Leu | Lys | Ala | Glu | Asn | Leu | Leu | |
| | | | | 185 | | | | | 190 | | | | | 195 | |
| Leu | Asp | Ala | Asn | Leu | Asn | Ile | Lys | Ile | Ala | Asp | Phe | Gly | Phe | Ser | |
| | | | | 200 | | | | | 205 | | | | | 210 | |
| Asn | Leu | Phe | Thr | Pro | Gly | Gln | Leu | Leu | Lys | Thr | Trp | Cys | Gly | Ser | |
| | | | | 215 | | | | | 220 | | | | | 225 | |
| Pro | Pro | Tyr | Ala | Ala | Pro | Glu | Leu | Phe | Glu | Gly | Lys | Glu | Tyr | Asp | |
| | | | | 230 | | | | | 235 | | | | | 240 | |
| Gly | Pro | Lys | Val | Asp | Ile | Trp | Ser | Leu | Gly | Val | Val | Leu | Tyr | Val | |
| | | | | 245 | | | | | 250 | | | | | 255 | |
| Leu | Val | Cys | Gly | Ala | Leu | Pro | Phe | Asp | Gly | Ser | Thr | Leu | Gln | Asn | |
| | | | | 260 | | | | | 265 | | | | | 270 | |
| Leu | Arg | Ala | Arg | Val | Leu | Ser | Gly | Lys | Phe | Arg | Ile | Pro | Phe | Phe | |
| | | | | 275 | | | | | 280 | | | | | 285 | |
| Met | Ser | Thr | Glu | Cys | Glu | His | Leu | Ile | Arg | His | Met | Leu | Val | Leu | |
| | | | | 290 | | | | | 295 | | | | | 300 | |
| Asp | Pro | Asn | Lys | Arg | Leu | Ser | Met | Glu | Gln | Ile | Cys | Lys | His | Lys | |
| | | | | 305 | | | | | 310 | | | | | 315 | |
| Trp | Met | Lys | Leu | Gly | Asp | Ala | Asp | Pro | Asn | Phe | Asp | Arg | Leu | Ile | |
| | | | | 320 | | | | | 325 | | | | | 330 | |
| Ala | Glu | Cys | Gln | Gln | Leu | Lys | Glu | Glu | Arg | Gln | Val | Asp | Pro | Leu | |
| | | | | 335 | | | | | 340 | | | | | 345 | |
| Asn | Glu | Asp | Val | Leu | Leu | Ala | Met | Glu | Asp | Met | Gly | Leu | Asp | Lys | |
| | | | | 350 | | | | | 355 | | | | | 360 | |
| Glu | Gln | Thr | Leu | Gln | Ser | Leu | Arg | Ser | Asp | Ala | Tyr | Asp | His | Tyr | |
| | | | | 365 | | | | | 370 | | | | | 375 | |
| Ser | Ala | Ile | Tyr | Ser | Leu | Leu | Cys | Asp | Arg | His | Lys | Arg | His | Lys | |
| | | | | 380 | | | | | 385 | | | | | 390 | |
| Thr | Leu | Arg | Leu | Gly | Ala | Leu | Pro | Ser | Met | Pro | Arg | Ala | Leu | Ala | |
| | | | | 395 | | | | | 400 | | | | | 405 | |
| Phe | Gln | Ala | Pro | Val | Asn | Ile | Gln | Ala | Glu | Gln | Ala | Gly | Thr | Ala | |
| | | | | 410 | | | | | 415 | | | | | 420 | |
| Met | Asn | Ile | Ser | Val | Pro | Gln | Val | Gln | Leu | Ile | Asn | Pro | Glu | Asn | |
| | | | | 425 | | | | | 430 | | | | | 435 | |
| Gln | Ile | Val | Glu | Pro | Asp | Gly | Thr | Leu | Asn | Leu | Asp | Ser | Asp | Glu | |
| | | | | 440 | | | | | 445 | | | | | 450 | |

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Glu | Glu | Pro | Ser | Pro | Glu | Ala | Leu | Val | Arg | Tyr | Leu | Ser | Met |
| | | | | 455 | | | | | 460 | | | | | 465 |
| Arg | Arg | His | Thr | Val | Gly | Val | Ala | Asp | Pro | Arg | Thr | Glu | Val | Met |
| | | | | 470 | | | | | 475 | | | | | 480 |
| Glu | Asp | Leu | Gln | Lys | Leu | Leu | Pro | Gly | Phe | Pro | Gly | Val | Asn | Pro |
| | | | | 485 | | | | | 490 | | | | | 495 |
| Gln | Ala | Pro | Phe | Leu | Gln | Val | Ala | Pro | Asn | Val | Asn | Phe | Met | His |
| | | | | 500 | | | | | 505 | | | | | 510 |
| Asn | Leu | Leu | Pro | Met | Gln | Asn | Leu | Gln | Pro | Thr | Gly | Gln | Leu | Glu |
| | | | | 515 | | | | | 520 | | | | | 525 |
| Tyr | Lys | Glu | Gln | Ser | Leu | Leu | Gln | Pro | Pro | Thr | Leu | Gln | Leu | Leu |
| | | | | 530 | | | | | 535 | | | | | 540 |
| Asn | Gly | Met | Gly | Pro | Leu | Gly | Arg | Arg | Ala | Ser | Asp | Gly | Gly | Ala |
| | | | | 545 | | | | | 550 | | | | | 555 |
| Asn | Ile | Gln | Leu | His | Ala | Gln | Gln | Leu | Leu | Lys | Arg | Pro | Arg | Gly |
| | | | | 560 | | | | | 565 | | | | | 570 |
| Pro | Ser | Pro | Leu | Val | Thr | Met | Thr | Pro | Ala | Val | Pro | Ala | Val | Thr |
| | | | | 575 | | | | | 580 | | | | | 585 |
| Pro | Val | Asp | Glu | Glu | Ser | Ser | Asp | Gly | Glu | Pro | Asp | Gln | Glu | Ala |
| | | | | 590 | | | | | 595 | | | | | 600 |
| Val | Gln | Arg | Tyr | Leu | Ala | Asn | Arg | Ser | Lys | Arg | His | Thr | Leu | Ala |
| | | | | 605 | | | | | 610 | | | | | 615 |
| Met | Thr | Asn | Pro | Thr | Ala | Glu | Ile | Pro | Pro | Asp | Leu | Gln | Arg | Gln |
| | | | | 620 | | | | | 625 | | | | | 630 |
| Leu | Gly | Gln | Gln | Pro | Phe | Arg | Ser | Arg | Val | Trp | Pro | Pro | His | Leu |
| | | | | 635 | | | | | 640 | | | | | 645 |
| Val | Pro | Asp | Gln | His | Arg | Ser | Thr | Tyr | Lys | Asp | Ser | Asn | Thr | Leu |
| | | | | 650 | | | | | 655 | | | | | 660 |
| His | Leu | Pro | Thr | Glu | Arg | Phe | Ser | Pro | Val | Arg | Arg | Phe | Ser | Asp |
| | | | | 665 | | | | | 670 | | | | | 675 |
| Gly | Ala | Ala | Ser | Ile | Gln | Ala | Phe | Lys | Ala | His | Leu | Glu | Lys | Met |
| | | | | 680 | | | | | 685 | | | | | 690 |
| Gly | Asn | Asn | Ser | Ser | Ile | Lys | Gln | Leu | Gln | Gln | Glu | Cys | Glu | Gln |
| | | | | 695 | | | | | 700 | | | | | 705 |
| Leu | Gln | Lys | Met | Tyr | Gly | Gly | Gln | Ile | Asp | Glu | Arg | Thr | Leu | Glu |
| | | | | 710 | | | | | 715 | | | | | 720 |
| Lys | Thr | Gln | Gln | Gln | His | Met | Leu | Tyr | Gln | Gln | Glu | Gln | His | His |
| | | | | 725 | | | | | 730 | | | | | 735 |
| Gln | Ile | Leu | Gln | Gln | Gln | Ile | Gln | Asp | Ser | Ile | Cys | Pro | Pro | Gln |
| | | | | 740 | | | | | 745 | | | | | 750 |
| Pro | Ser | Pro | Pro | Leu | Gln | Ala | Ala | Cys | Glu | Asn | Gln | Pro | Ala | Leu |
| | | | | 755 | | | | | 760 | | | | | 765 |
| Leu | Thr | His | Gln | Leu | Gln | Arg | Leu | Arg | Ile | Gln | Pro | Ser | Ser | Pro |
| | | | | 770 | | | | | 775 | | | | | 780 |
| Pro | Pro | Asn | His | Pro | Asn | Asn | His | Leu | Phe | Arg | Gln | Pro | Ser | Asn |
| | | | | 785 | | | | | 790 | | | | | 795 |
| Ser | Pro | Pro | Pro | Met | Ser | Ser | Ala | Met | Ile | Gln | Pro | His | Gly | Ala |
| | | | | 800 | | | | | 805 | | | | | 810 |
| Ala | Ser | Ser | Ser | Gln | Phe | Gln | Gly | Leu | Pro | Ser | Arg | Ser | Ala | Ile |
| | | | | 815 | | | | | 820 | | | | | 825 |
| Phe | Gln | Gln | Gln | Pro | Glu | Asn | Cys | Ser | Ser | Pro | Pro | Asn | Val | Ala |
| | | | | 830 | | | | | 835 | | | | | 840 |
| Leu | Thr | Cys | Leu | Gly | Met | Gln | Gln | Pro | Ala | Gln | Ser | Gln | Gln | Val |
| | | | | 845 | | | | | 850 | | | | | 855 |
| Thr | Ile | Gln | Val | Gln | Glu | Pro | Val | Asp | Met | Leu | Ser | Asn | Met | Pro |
| | | | | 860 | | | | | 865 | | | | | 870 |

| | | | |
|---|------|------|------|
| Gly Thr Ala Ala Gly Ser Ser Gly Arg Gly Ile Ser Ile Ser Pro | 875 | 880 | 885 |
| Ser Ala Gly Gln Met Gln Met Gln His Arg Thr Asn Leu Met Ala | 890 | 895 | 900 |
| Thr Leu Ser Tyr Gly His Arg Pro Leu Ser Lys Gln Leu Ser Ala | 905 | 910 | 915 |
| Asp Ser Ala Glu Ala His Ser Leu Asn Val Asn Arg Phe Ser Pro | 920 | 925 | 930 |
| Ala Asn Tyr Asp Gln Ala His Leu His Pro His Leu Phe Ser Asp | 935 | 940 | 945 |
| Gln Ser Arg Gly Ser Pro Ser Ser Tyr Ser Pro Ser Thr Gly Val | 950 | 955 | 960 |
| Gly Phe Ser Pro Thr Gln Ala Leu Lys Val Pro Pro Leu Asp Gln | 965 | 970 | 975 |
| Phe Pro Thr Phe Pro Pro Ser Ala His Gln Gln Pro Pro His Tyr | 980 | 985 | 990 |
| Thr Thr Ser Ala Leu Gln Gln Ala Leu Leu Ser Pro Thr Pro Pro | 995 | 1000 | 1005 |
| Asp Tyr Thr Arg His Gln Gln Val Pro His Ile Leu Gln Gly Leu | 1010 | 1015 | 1020 |
| Leu Ser Pro Arg His Ser Leu Thr Gly His Ser Asp Ile Arg Leu | 1025 | 1030 | 1035 |
| Pro Pro Thr Glu Phe Ala Gln Leu Ile Lys Arg Gln Gln Gln Gln | 1040 | 1045 | 1050 |
| Arg Gln Gln Gln Gln Gln Gln Gln Gln Gln Glu Tyr Gln Glu | 1055 | 1060 | 1065 |
| Leu Phe Arg His Met Asn Gln Gly Asp Ala Gly Ser Leu Ala Pro | 1070 | 1075 | 1080 |
| Ser Leu Gly Gly Gln Ser Met Thr Glu Arg Gln Ala Leu Ser Tyr | 1085 | 1090 | 1095 |
| Gln Asn Ala Asp Ser Tyr His His His Thr Ser Pro Gln His Leu | 1100 | 1105 | 1110 |
| Leu Gln Ile Arg Ala Gln Glu Cys Val Ser Gln Ala Ser Ser Pro | 1115 | 1120 | 1125 |
| Thr Pro Pro His Gly Tyr Ala His Gln Pro Ala Leu Met His Ser | 1130 | 1135 | 1140 |
| Glu Ser Met Glu Glu Asp Cys Ser Cys Glu Gly Ala Lys Asp Gly | 1145 | 1150 | 1155 |
| Phe Gln Asp Ser Lys Ser Ser Ser Thr Leu Thr Lys Gly Cys His | 1160 | 1165 | 1170 |
| Asp Ser Pro Leu Leu Ser Thr Gly Gly Pro Gly Asp Pro Glu | 1175 | 1180 | 1185 |
| Ser Leu Leu Gly Thr Val Ser His Ala Gln Glu Leu Gly Ile His | 1190 | 1195 | 1200 |
| Pro Tyr Gly His Gln Pro Thr Ala Ala Phe Ser Lys Asn Lys Val | 1205 | 1210 | 1215 |
| Pro Ser Arg Glu Pro Val Ile Gly Asn Cys Met Asp Arg Ser Ser | 1220 | 1225 | 1230 |
| Pro Gly Gln Ala Val Glu Leu Pro Asp His Asn Gly Leu Gly Tyr | 1235 | 1240 | 1245 |
| Pro Ala Arg Pro Ser Val His Glu His His Arg Pro Arg Ala Leu | 1250 | 1255 | 1260 |
| Gln Arg His His Thr Ile Gln Asn Ser Asp Asp Ala Tyr Val Gln | 1265 | 1270 | 1275 |
| Leu Asp Asn Leu Pro Gly Met Ser Leu Val Ala Gly Lys Ala Leu | 1280 | 1285 | 1290 |

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Ser Ser Ala Arg Met Ser Asp Ala Val Leu Ser Gln Ser Ser Leu
      1295                      1300                      1305
Met Gly Ser Gln Gln Phe Gln Asp Gly Glu Asn Glu Glu Cys Gly
      1310                      1315                      1320
Ala Ser Leu Gly Gly His Glu His Pro Asp Leu Ser Asp Gly Ser
      1325                      1330                      1335
Gln His Leu Asn Ser Ser Cys Tyr Pro Ser Thr Cys Ile Thr Asp
      1340                      1345                      1350
Ile Leu Leu Ser Tyr Lys His Pro Glu Val Ser Phe Ser Met Glu
      1355                      1360                      1365
Gln Ala Gly Val

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Ser Cys Arg Thr Ser Asn Arg Lys Ser Leu Ile Gly Asn Gly Gln
      35          40          45
Ser Pro Ala Leu Pro Arg Pro His Ser Pro Leu Ser Ala His Ala
      50          55          60
Gly Asn Ser Pro Gln Asp Ser Pro Arg Asn Phe Ser Pro Ser Ala
      65          70          75
Ser Ala His Phe Ser Phe Ala Arg Arg Thr Asp Gly Arg Arg Trp
      80          85          90
Ser Leu Ala Ser Leu Pro Ser Ser Gly Tyr Gly Thr Asn Thr Pro
      95          100         105
Ser Ser Thr Val Ser Ser Ser Cys Ser Ser Gln Glu Lys Leu His
      110         115         120
Gln Leu Pro Tyr Gln Pro Thr Pro Asp Glu Leu His Phe Leu Ser
      125         130         135
Lys His Phe Cys Thr Thr Glu Ser Ile Ala Thr Glu Asn Arg Cys
      140         145         150
Arg Asn Thr Pro Met Arg Pro Arg Ser Arg Ser Leu Ser Pro Gly
      155         160         165
Arg Ser Pro Ala Cys Cys Asp His Glu Ile Ile Met Met Asn His
      170         175         180
Val Tyr Lys Glu Arg Phe Pro Lys Ala Thr Ala Gln Met Glu Glu
      185         190         195
Arg Leu Lys Glu Ile Ile Thr Ser Tyr Ser Pro Asp Asn Val Leu
      200         205         210
Pro Leu Ala Asp Gly Val Leu Ser Phe Thr His His Gln Ile Ile
      215         220         225
Glu Leu Ala Arg Asp Cys Leu Asp Lys Ser His Gln Gly Leu Ile
      230         235         240
Thr Ser Arg Tyr Phe Leu Glu Leu Gln His Lys Leu Asp Lys Leu

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| | | | |
|-----------------|---------------------|---------------------|-----|
| | 245 | 250 | 255 |
| Leu Gln Glu Ala | His Asp Arg Ser Glu | Ser Gly Glu Leu Ala | Phe |
| | 260 | 265 | 270 |
| Ile Lys Gln Leu | Val Arg Lys Ile Leu | Ile Val Ile Ala Arg | Pro |
| | 275 | 280 | 285 |
| Ala Arg Leu Leu | Glu Cys Leu Glu Phe | Asp Pro Glu Glu Phe | Tyr |
| | 290 | 295 | 300 |
| Tyr Leu Leu Glu | Ala Ala Glu Gly His | Ala Lys Glu Gly Gln | Gly |
| | 305 | 310 | 315 |
| Ile Lys Thr Asp | Ile Pro Arg Tyr Ile | Ile Ser Gln Leu Gly | Leu |
| | 320 | 325 | 330 |
| Asn Lys Asp Pro | Leu Glu Glu Met Ala | His Leu Gly Asn Tyr | Asp |
| | 335 | 340 | 345 |
| Ser Gly Thr Ala | Glu Thr Pro Glu Thr | Asp Glu Ser Val Ser | Ser |
| | 350 | 355 | 360 |
| Ser Asn Ala Ser | Leu Lys Leu Arg Arg | Lys Pro Arg Glu Ser | Asp |
| | 365 | 370 | 375 |
| Phe Glu Thr Ile | Lys Leu Ile Ser Asn | Gly Ala Tyr Gly Ala | Val |
| | 380 | 385 | 390 |
| Tyr Phe Val Arg | His Lys Glu Ser Arg | Gln Arg Phe Ala Met | Lys |
| | 395 | 400 | 405 |
| Lys Ile Asn Lys | Gln Asn Leu Ile Leu | Arg Asn Gln Ile Gln | Gln |
| | 410 | 415 | 420 |
| Ala Phe Val Glu | Arg Asp Ile Leu Thr | Phe Ala Glu Asn Pro | Phe |
| | 425 | 430 | 435 |
| Val Val Ser Met | Tyr Cys Ser Phe Glu | Thr Arg Arg His Leu | Cys |
| | 440 | 445 | 450 |
| Met Val Met Glu | Tyr Val Glu Gly Gly | Asp Cys Ala Thr Leu | Met |
| | 455 | 460 | 465 |
| Lys Asn Met Gly | Pro Leu Pro Val Asp | Met Ala Arg Met Tyr | Phe |
| | 470 | 475 | 480 |
| Ala Glu Thr Val | Leu Ala Leu Glu Tyr | Leu His Asn Tyr Gly | Ile |
| | 485 | 490 | 495 |
| Val His Arg Asp | Leu Lys Pro Asp Asn | Leu Leu Val Thr Ser | Met |
| | 500 | 505 | 510 |
| Gly His Ile Lys | Leu Thr Asp Phe Gly | Leu Ser Lys Val Gly | Leu |
| | 515 | 520 | 525 |
| Met Ser Met Thr | Thr Asn Leu Tyr Glu | Gly His Ile Glu Lys | Asp |
| | 530 | 535 | 540 |
| Ala Arg Glu Phe | Leu Asp Lys Gln Val | Cys Gly Thr Pro Glu | Tyr |
| | 545 | 550 | 555 |
| Ile Ala Pro Glu | Val Ile Leu Arg Gln | Gly Tyr Gly Lys Pro | Val |
| | 560 | 565 | 570 |
| Asp Trp Trp Ala | Met Gly Ile Ile Leu | Tyr Glu Phe Leu Val | Gly |
| | 575 | 580 | 585 |
| Cys Val Pro Phe | Phe Gly Asp Thr Pro | Glu Glu Leu Phe Gly | Gln |
| | 590 | 595 | 600 |
| Val Ile Ser Asp | Glu Ile Asn Trp Pro | Glu Lys Asp Glu Ala | Pro |
| | 605 | 610 | 615 |
| Pro Pro Asp Ala | Gln Asp Leu Ile Thr | Leu Leu Leu Arg Gln | Asn |
| | 620 | 625 | 630 |
| Pro Leu Glu Arg | Leu Gly Thr Gly Gly | Ala Tyr Glu Val Lys | Gln |
| | 635 | 640 | 645 |
| His Arg Phe Phe | Arg Ser Leu Asp Trp | Asn Ser Leu Leu Arg | Gln |
| | 650 | 655 | 660 |
| Lys Ala Glu Phe | Ile Pro Gln Leu Glu | Ser Glu Asp Asp Thr | Ser |

| | | | | | |
|-------------------------------------|------|-------------------------|------|--|------|
| | 665 | | 670 | | 675 |
| Tyr Phe Asp Thr Arg Ser Glu Lys Tyr | | His His Met Glu Thr Glu | | | |
| | 680 | | 685 | | 690 |
| Glu Glu Asp Asp Thr Asn Asp Glu Asp | | Phe Asn Val Glu Ile Arg | | | |
| | 695 | | 700 | | 705 |
| Gln Phe Ser Ser Cys Ser His Arg Phe | | Ser Lys Val Phe Ser Ser | | | |
| | 710 | | 715 | | 720 |
| Ile Asp Arg Ile Thr Gln Asn Ser Ala | | Glu Glu Lys Glu Asp Ser | | | |
| | 725 | | 730 | | 735 |
| Val Asp Lys Thr Lys Ser Thr Thr Leu | | Pro Ser Thr Glu Thr Leu | | | |
| | 740 | | 745 | | 750 |
| Ser Trp Ser Ser Glu Tyr Ser Glu Met | | Gln Gln Leu Ser Thr Ser | | | |
| | 755 | | 760 | | 765 |
| Asn Ser Ser Asp Thr Glu Ser Asn Arg | | His Lys Leu Ser Ser Gly | | | |
| | 770 | | 775 | | 780 |
| Leu Leu Pro Lys Leu Ala Ile Ser Thr | | Glu Gly Glu Gln Asp Glu | | | |
| | 785 | | 790 | | 795 |
| Ala Ala Ser Cys Pro Gly Asp Pro His | | Glu Glu Pro Gly Lys Pro | | | |
| | 800 | | 805 | | 810 |
| Ala Leu Pro Pro Glu Glu Cys Ala Gln | | Glu Glu Pro Glu Val Thr | | | |
| | 815 | | 820 | | 825 |
| Thr Pro Ala Ser Thr Ile Ser Ser Ser | | Thr Leu Ser Val Gly Ser | | | |
| | 830 | | 835 | | 840 |
| Phe Ser Glu His Leu Asp Gln Ile Asn | | Gly Arg Ser Glu Cys Val | | | |
| | 845 | | 850 | | 855 |
| Asp Ser Thr Asp Asn Ser Ser Lys Pro | | Ser Ser Glu Pro Ala Ser | | | |
| | 860 | | 865 | | 870 |
| His Met Ala Arg Gln Arg Leu Glu Ser | | Thr Glu Lys Lys Lys Ile | | | |
| | 875 | | 880 | | 885 |
| Ser Gly Lys Val Thr Lys Ser Leu Ser | | Ala Ser Ala Leu Ser Leu | | | |
| | 890 | | 895 | | 900 |
| Met Ile Pro Gly Asp Met Phe Ala Val | | Ser Pro Leu Gly Ser Pro | | | |
| | 905 | | 910 | | 915 |
| Met Ser Pro His Ser Leu Ser Ser Asp | | Pro Ser Ser Ser Arg Asp | | | |
| | 920 | | 925 | | 930 |
| Ser Ser Pro Ser Arg Asp Ser Ser Ala | | Ala Ser Ala Ser Pro His | | | |
| | 935 | | 940 | | 945 |
| Gln Pro Ile Val Ile His Ser Ser Gly | | Lys Asn Tyr Gly Phe Thr | | | |
| | 950 | | 955 | | 960 |
| Ile Arg Ala Ile Arg Val Tyr Val Gly | | Ser Asp Ile Tyr Thr | | | |
| | 965 | | 970 | | 975 |
| Val His His Ile Val Trp Asn Val Glu | | Glu Gly Ser Pro Ala Cys | | | |
| | 980 | | 985 | | 990 |
| Gln Ala Gly Leu Lys Ala Gly Asp Leu | | Ile Thr Pro Ile Asn Gly | | | |
| | 995 | | 1000 | | 1005 |
| Glu Pro Val His Gly Leu Val His Thr | | Glu Val Ile Glu Leu Leu | | | |
| | 1010 | | 1015 | | 1020 |
| Leu Lys Ser Gly Asn Lys Val Ser Ile | | Thr Thr Thr Pro Phe Glu | | | |
| | 1025 | | 1030 | | 1035 |
| Asn Thr Ser Ile Lys Thr Gly Pro Ala | | Arg Arg Asn Ser Tyr Lys | | | |
| | 1040 | | 1045 | | 1050 |
| Ser Arg Met Val Arg Arg Ser Lys Lys | | Ser Lys Lys Lys Glu Ser | | | |
| | 1055 | | 1060 | | 1065 |
| Leu Glu Arg Arg Arg Ser Leu Phe Lys | | Lys Leu Ala Lys Gln Pro | | | |
| | 1070 | | 1075 | | 1080 |
| Ser Pro Leu Leu His Thr Ser Arg Ser | | Phe Ser Cys Leu Asn Arg | | | |

| | | | | | |
|---|------|--|------|--|------|
| | 1085 | | 1090 | | 1095 |
| Ser Leu Ser Ser Gly Glu Ser Leu Pro Gly Ser Pro Thr His Ser | | | | | |
| | 1100 | | 1105 | | 1110 |
| Leu Ser Pro Arg Ser Pro Thr Pro Ser Tyr Arg Ser Thr Pro Asp | | | | | |
| | 1115 | | 1120 | | 1125 |
| Phe Pro Ser Gly Thr Asn Ser Ser Gln Ser Ser Ser Pro Ser Ser | | | | | |
| | 1130 | | 1135 | | 1140 |
| Ser Ala Pro Asn Ser Pro Ala Gly Ser Gly His Ile Arg Pro Ser | | | | | |
| | 1145 | | 1150 | | 1155 |
| Thr Leu His Gly Leu Ala Pro Lys Leu Gly Gly Gln Arg Tyr Arg | | | | | |
| | 1160 | | 1165 | | 1170 |
| Ser Gly Arg Arg Lys Ser Ala Gly Asn Ile Pro Leu Ser Pro Leu | | | | | |
| | 1175 | | 1180 | | 1185 |
| Ala Arg Thr Pro Ser Pro Thr Pro Gln Pro Thr Ser Pro Gln Arg | | | | | |
| | 1190 | | 1195 | | 1200 |
| Ser Pro Ser Pro Leu Leu Gly His Ser Leu Gly Asn Ser Lys Ile | | | | | |
| | 1205 | | 1210 | | 1215 |
| Ala Gln Ala Phe Pro Ser Lys Met His Ser Pro Pro Thr Ile Val | | | | | |
| | 1220 | | 1225 | | 1230 |
| Arg His Ile Val Arg Pro Lys Ser Ala Glu Pro Pro Arg Ser Pro | | | | | |
| | 1235 | | 1240 | | 1245 |
| Leu Leu Lys Arg Val Gln Ser Glu Glu Lys Leu Ser Pro Ser Tyr | | | | | |
| | 1250 | | 1255 | | 1260 |
| Gly Ser Asp Lys Lys His Leu Cys Ser Arg Lys His Ser Leu Glu | | | | | |
| | 1265 | | 1270 | | 1275 |
| Val Thr Gln Glu Glu Val Gln Arg Glu Gln Ser Gln Arg Glu Ala | | | | | |
| | 1280 | | 1285 | | 1290 |
| Pro Leu Gln Ser Leu Asp Glu Asn Val Cys Asp Val Pro Pro Leu | | | | | |
| | 1295 | | 1300 | | 1305 |
| Ser Arg Ala Arg Pro Val Glu Gln Gly Cys Leu Lys Arg Pro Val | | | | | |
| | 1310 | | 1315 | | 1320 |
| Ser Arg Lys Val Gly Arg Gln Glu Ser Val Asp Asp Leu Asp Arg | | | | | |
| | 1325 | | 1330 | | 1335 |
| Asp Lys Leu Lys Ala Lys Val Val Val Lys Lys Ala Asp Gly Phe | | | | | |
| | 1340 | | 1345 | | 1350 |
| Pro Glu Lys Gln Glu Ser His Gln Lys Ser His Gly Pro Gly Ser | | | | | |
| | 1355 | | 1360 | | 1365 |
| Asp Leu Glu Asn Phe Ala Leu Phe Lys Leu Glu Glu Arg Glu Lys | | | | | |
| | 1370 | | 1375 | | 1380 |
| Lys Val Tyr Pro Lys Ala Val Glu Arg Ser Ser Thr Phe Glu Asn | | | | | |
| | 1385 | | 1390 | | 1395 |
| Lys Ala Ser Met Gln Glu Ala Pro Pro Leu Gly Ser Leu Leu Lys | | | | | |
| | 1400 | | 1405 | | 1410 |
| Asp Ala Leu His Lys Gln Ala Ser Val Arg Ala Ser Glu Gly Ala | | | | | |
| | 1415 | | 1420 | | 1425 |
| Met Ser Asp Gly Pro Val Pro Ala Glu His Arg Gln Gly Gly Gly | | | | | |
| | 1430 | | 1435 | | 1440 |
| Asp Phe Arg Arg Ala Pro Ala Pro Gly Thr Leu Gln Asp Gly Leu | | | | | |
| | 1445 | | 1450 | | 1455 |
| Cys His Ser Leu Asp Arg Gly Ile Ser Gly Lys Gly Glu Gly Thr | | | | | |
| | 1460 | | 1465 | | 1470 |
| Glu Lys Ser Ser Gln Ala Lys Glu Leu Leu Arg Cys Glu Lys Leu | | | | | |
| | 1475 | | 1480 | | 1485 |
| Asp Ser Lys Leu Ala Asn Ile Asp Tyr Leu Arg Lys Lys Met Ser | | | | | |
| | 1490 | | 1495 | | 1500 |
| Leu Glu Asp Lys Glu Asp Asn Leu Cys Pro Val Leu Lys Pro Lys | | | | | |

| | | |
|---|------|------|
| 1505 | 1510 | 1515 |
| Met Thr Ala Gly Ser His Glu Cys Leu Pro Gly Asn Pro Val Arg | | |
| 1520 | 1525 | 1530 |
| Pro Thr Gly Gly Gln Gln Glu Pro Pro Pro Ala Ser Glu Ser Arg | | |
| 1535 | 1540 | 1545 |
| Ala Phe Val Ser Ser Thr His Ala Ala Gln Met Ser Ala Val Ser | | |
| 1550 | 1555 | 1560 |
| Phe Val Pro Leu Lys Ala Leu Thr Gly Arg Val Asp Ser Gly Thr | | |
| 1565 | 1570 | 1575 |
| Glu Lys Pro Gly Leu Val Ala Pro Glu Ser Pro Val Arg Lys Ser | | |
| 1580 | 1585 | 1590 |
| Pro Ser Glu Tyr Lys Leu Glu Gly Arg Ser Val Ser Cys Leu Lys | | |
| 1595 | 1600 | 1605 |
| Pro Ile Glu Gly Thr Leu Asp Ile Ala Leu Leu Ser Gly Pro Gln | | |
| 1610 | 1615 | 1620 |
| Ala Ser Lys Thr Glu Leu Pro Ser Pro Glu Ser Ala Gln Ser Pro | | |
| 1625 | 1630 | 1635 |
| Ser Pro Ser Gly Asp Val Arg Ala Ser Val Pro Pro Val Leu Pro | | |
| 1640 | 1645 | 1650 |
| Ser Ser Ser Gly Lys Lys Asn Asp Thr Thr Ser Ala Arg Glu Leu | | |
| 1655 | 1660 | 1665 |
| Ser Pro Ser Ser Leu Lys Met Asn Lys Ser Tyr Leu Leu Glu Pro | | |
| 1670 | 1675 | 1680 |
| Trp Phe Leu Pro Pro Ser Arg Gly Leu Gln Asn Ser Pro Ala Val | | |
| 1685 | 1690 | 1695 |
| Ser Leu Pro Asp Pro Glu Phe Lys Arg Asp Arg Lys Gly Pro His | | |
| 1700 | 1705 | 1710 |
| Pro Thr Ala Arg Ser Pro Gly Thr Val Met Glu Ser Asn Pro Gln | | |
| 1715 | 1720 | 1725 |
| Gln Arg Glu Gly Ser Ser Pro Lys His Gln Asp His Thr Thr Asp | | |
| 1730 | 1735 | 1740 |
| Pro Lys Leu Leu Thr Cys Leu Gly Gln Asn Leu His Ser Pro Asp | | |
| 1745 | 1750 | 1755 |
| Leu Ala Arg Pro Arg Cys Pro Leu Pro Pro Glu Ala Ser Pro Ser | | |
| 1760 | 1765 | 1770 |
| Arg Glu Lys Pro Gly Leu Arg Glu Ser Ser Glu Arg Gly Pro Pro | | |
| 1775 | 1780 | 1785 |
| Thr Ala Arg Ser Glu Arg Ser Ala Ala Arg Ala Asp Thr Cys Arg | | |
| 1790 | 1795 | 1800 |
| Glu Pro Ser Met Glu Leu Cys Phe Pro Glu Thr Ala Lys Thr Ser | | |
| 1805 | 1810 | 1815 |
| Asp Asn Ser Lys Asn Leu Leu Ser Val Gly Arg Thr His Pro Asp | | |
| 1820 | 1825 | 1830 |
| Phe Tyr Thr Gln Thr Gln Ala Met Glu Lys Ala Trp Ala Pro Gly | | |
| 1835 | 1840 | 1845 |
| Gly Lys Thr Asn His Lys Asp Gly Pro Gly Glu Ala Arg Pro Pro | | |
| 1850 | 1855 | 1860 |
| Pro Arg Asp Asn Ser Ser Leu His Ser Ala Gly Ile Pro Cys Glu | | |
| 1865 | 1870 | 1875 |
| Lys Glu Leu Gly Lys Val Arg Arg Gly Val Glu Pro Lys Pro Glu | | |
| 1880 | 1885 | 1890 |
| Ala Leu Leu Ala Arg Ser Leu Gln Pro Pro Gly Ile Glu Ser | | |
| 1895 | 1900 | 1905 |
| Glu Lys Ser Glu Lys Leu Ser Ser Phe Pro Ser Leu Gln Lys Asp | | |
| 1910 | 1915 | 1920 |
| Gly Ala Lys Glu Pro Glu Arg Lys Glu Gln Pro Leu Gln Arg His | | |

| | | | | | |
|---|------|--|------|--|------|
| | 1925 | | 1930 | | 1935 |
| Pro Ser Ser Ile Pro Pro Pro Pro Leu Thr Ala Lys Asp Leu Ser | | | | | |
| | 1940 | | 1945 | | 1950 |
| Ser Pro Ala Ala Arg Gln His Cys Ser Ser Pro Ser His Ala Ser | | | | | |
| | 1955 | | 1960 | | 1965 |
| Gly Arg Glu Pro Gly Ala Lys Pro Ser Thr Ala Glu Pro Ser Ser | | | | | |
| | 1970 | | 1975 | | 1980 |
| Ser Pro Gln Asp Pro Pro Lys Pro Val Ala Ala His Ser Glu Ser | | | | | |
| | 1985 | | 1990 | | 1995 |
| Ser Ser His Lys Pro Arg Pro Gly Pro Asp Pro Gly Pro Pro Lys | | | | | |
| | 2000 | | 2005 | | 2010 |
| Thr Lys His Pro Asp Arg Ser Leu Ser Ser Gln Lys Pro Ser Val | | | | | |
| | 2015 | | 2020 | | 2025 |
| Gly Ala Thr Lys Gly Lys Glu Pro Ala Thr Gln Ser Leu Gly Gly | | | | | |
| | 2030 | | 2035 | | 2040 |
| Ser Ser Arg Glu Gly Lys Gly His Ser Lys Ser Gly Pro Asp Val | | | | | |
| | 2045 | | 2050 | | 2055 |
| Phe Pro Ala Thr Pro Gly Ser Gln Asn Lys Ala Ser Asp Gly Ile | | | | | |
| | 2060 | | 2065 | | 2070 |
| Gly Gln Gly Glu Gly Gly Pro Ser Val Pro Leu His Thr Asp Arg | | | | | |
| | 2075 | | 2080 | | 2085 |
| Ala Pro Leu Asp Ala Lys Pro Gln Pro Thr Ser Gly Gly Arg Pro | | | | | |
| | 2090 | | 2095 | | 2100 |
| Leu Glu Val Leu Glu Lys Pro Val His Leu Pro Arg Pro Gly His | | | | | |
| | 2105 | | 2110 | | 2115 |
| Pro Gly Pro Ser Glu Pro Ala Asp Gln Lys Leu Ser Ala Val Gly | | | | | |
| | 2120 | | 2125 | | 2130 |
| Glu Lys Gln Thr Leu Ser Pro Lys His Pro Lys Pro Ser Thr Val | | | | | |
| | 2135 | | 2140 | | 2145 |
| Lys Asp Cys Pro Thr Leu Cys Lys Gln Thr Asp Asn Arg Gln Thr | | | | | |
| | 2150 | | 2155 | | 2160 |
| Asp Lys Ser Pro Ser Gln Pro Ala Ala Asn Thr Asp Arg Arg Ala | | | | | |
| | 2165 | | 2170 | | 2175 |
| Glu Gly Lys Lys Cys Thr Glu Ala Leu Tyr Ala Pro Ala Glu Gly | | | | | |
| | 2180 | | 2185 | | 2190 |
| Asp Lys Leu Glu Ala Gly Leu Ser Phe Val His Ser Glu Asn Arg | | | | | |
| | 2195 | | 2200 | | 2205 |
| Leu Lys Gly Ala Glu Arg Pro Ala Ala Gly Val Gly Lys Gly Phe | | | | | |
| | 2210 | | 2215 | | 2220 |
| Pro Glu Ala Arg Gly Lys Gly Pro Gly Pro Gln Lys Pro Pro Thr | | | | | |
| | 2225 | | 2230 | | 2235 |
| Glu Ala Asp Lys Pro Asn Gly Met Lys Arg Ser Pro Ser Ala Thr | | | | | |
| | 2240 | | 2245 | | 2250 |
| Gly Gln Ser Ser Phe Arg Ser Thr Ala Leu Pro Glu Lys Ser Leu | | | | | |
| | 2255 | | 2260 | | 2265 |
| Ser Cys Ser Ser Ser Phe Pro Glu Thr Arg Ala Gly Val Arg Glu | | | | | |
| | 2270 | | 2275 | | 2280 |
| Ala Ser Ala Ala Ser Ser Asp Thr Ser Ser Ala Lys Ala Ala Gly | | | | | |
| | 2285 | | 2290 | | 2295 |
| Gly Met Leu Glu Leu Pro Ala Pro Ser Asn Arg Asp His Arg Lys | | | | | |
| | 2300 | | 2305 | | 2310 |
| Ala Gln Pro Ala Gly Glu Gly Arg Thr His Met Thr Lys Ser Asp | | | | | |
| | 2315 | | 2320 | | 2325 |
| Ser Leu Pro Ser Phe Arg Val Ser Thr Leu Pro Leu Glu Ser His | | | | | |
| | 2330 | | 2335 | | 2340 |
| His Pro Asp Pro Asn Thr Met Gly Gly Ala Ser His Arg Asp Arg | | | | | |

| | | | | | | | | | | | | | | |
|-----|------|-----|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| | 2345 | | 2350 | | 2355 | | | | | | | | | |
| Ala | Leu | Ser | Val | Thr | Ala | Thr | Val | Gly | Glu | Thr | Lys | Gly | Lys | Asp |
| | 2360 | | 2365 | | 2370 | | | | | | | | | |
| Pro | Ala | Pro | Ala | Gln | Pro | Pro | Pro | Ala | Arg | Lys | Gln | Asn | Val | Gly |
| | 2375 | | 2380 | | 2385 | | | | | | | | | |
| Arg | Asp | Val | Thr | Lys | Pro | Ser | Pro | Ala | Pro | Asn | Thr | Asp | Arg | Pro |
| | 2390 | | 2395 | | 2400 | | | | | | | | | |
| Ile | Ser | Leu | Ser | Asn | Glu | Lys | Asp | Phe | Val | Val | Arg | Gln | Arg | Arg |
| | 2405 | | 2410 | | 2415 | | | | | | | | | |
| Gly | Lys | Glu | Ser | Leu | Arg | Ser | Ser | Pro | His | Lys | Lys | Ala | Leu | |
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<211> 2135

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

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<400> 9

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| Met | Ser | Gly | Gly | Ala | Ala | Glu | Lys | Gln | Ser | Ser | Thr | Pro | Gly | Ser |
| 1 | | | | 5 | | | | | 10 | | | | | 15 |
| Leu | Phe | Leu | Ser | Pro | Pro | Ala | Pro | Ala | Pro | Lys | Asn | Gly | Ser | Ser |
| | | | | 20 | | | | | 25 | | | | | 30 |
| Ser | Asp | Ser | Ser | Val | Gly | Glu | Lys | Leu | Gly | Ala | Ala | Ala | Ala | Asp |
| | | | | 35 | | | | | 40 | | | | | 45 |
| Ala | Val | Thr | Gly | Arg | Thr | Glu | Glu | Tyr | Arg | Arg | Arg | Arg | His | Thr |
| | | | | 50 | | | | | 55 | | | | | 60 |
| Met | Asp | Lys | Asp | Ser | Arg | Gly | Ala | Ala | Ala | Thr | Thr | Thr | Thr | Thr |
| | | | | 65 | | | | | 70 | | | | | 75 |
| Glu | His | Arg | Phe | Phe | Arg | Arg | Ser | Val | Ile | Cys | Asp | Ser | Asn | Ala |
| | | | | 80 | | | | | 85 | | | | | 90 |
| Thr | Ala | Leu | Glu | Leu | Pro | Gly | Leu | Pro | Leu | Ser | Leu | Pro | Gln | Pro |
| | | | | 95 | | | | | 100 | | | | | 105 |
| Ser | Ile | Pro | Ala | Ala | Val | Pro | Gln | Ser | Ala | Pro | Pro | Glu | Pro | His |
| | | | | 110 | | | | | 115 | | | | | 120 |
| Arg | Glu | Glu | Thr | Val | Thr | Ala | Thr | Ala | Thr | Ser | Gln | Val | Ala | Gln |
| | | | | 125 | | | | | 130 | | | | | 135 |
| Gln | Pro | Pro | Ala | Ala | Ala | Ala | Pro | Gly | Glu | Gln | Ala | Val | Ala | Gly |
| | | | | 140 | | | | | 145 | | | | | 150 |
| Pro | Ala | Pro | Ser | Thr | Val | Pro | Ser | Ser | Thr | Ser | Lys | Asp | Arg | Pro |
| | | | | 155 | | | | | 160 | | | | | 165 |
| Val | Ser | Gln | Pro | Ser | Leu | Val | Gly | Ser | Lys | Glu | Glu | Pro | Pro | Pro |
| | | | | 170 | | | | | 175 | | | | | 180 |
| Ala | Arg | Ser | Gly | Ser | Gly | Gly | Gly | Ser | Ala | Lys | Glu | Pro | Gln | Glu |
| | | | | 185 | | | | | 190 | | | | | 195 |
| Glu | Arg | Ser | Gln | Gln | Gln | Asp | Asp | Ile | Glu | Glu | Leu | Glu | Thr | Lys |
| | | | | 200 | | | | | 205 | | | | | 210 |
| Ala | Val | Gly | Met | Ser | Asn | Asp | Gly | Arg | Phe | Leu | Lys | Phe | Asp | Ile |
| | | | | 215 | | | | | 220 | | | | | 225 |
| Glu | Ile | Gly | Arg | Gly | Ser | Phe | Lys | Thr | Val | Tyr | Lys | Gly | Leu | Asp |
| | | | | 230 | | | | | 235 | | | | | 240 |
| Thr | Glu | Thr | Thr | Val | Glu | Val | Ala | Trp | Cys | Glu | Leu | Gln | Asp | Arg |
| | | | | 245 | | | | | 250 | | | | | 255 |

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Leu | Thr | Lys | Ser | Glu | Arg | Gln | Arg | Phe | Lys | Glu | Glu | Ala | Glu |
| | | | | 260 | | | | | 265 | | | | | 270 |
| Met | Leu | Lys | Gly | Leu | Gln | His | Pro | Asn | Ile | Val | Arg | Phe | Tyr | Asp |
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| Ser | Trp | Glu | Ser | Thr | Val | Lys | Gly | Lys | Lys | Cys | Ile | Val | Leu | Val |
| | | | | 290 | | | | | 295 | | | | | 300 |
| Thr | Glu | Leu | Met | Thr | Ser | Gly | Thr | Leu | Lys | Thr | Tyr | Leu | Lys | Arg |
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| Phe | Lys | Val | Met | Lys | Ile | Lys | Val | Leu | Arg | Ser | Trp | Cys | Arg | Gln |
| | | | | 320 | | | | | 325 | | | | | 330 |
| Ile | Leu | Lys | Gly | Leu | Gln | Phe | Leu | His | Thr | Arg | Thr | Pro | Pro | Ile |
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| Ile | His | Arg | Asp | Leu | Lys | Cys | Asp | Asn | Ile | Phe | Ile | Thr | Gly | Pro |
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| Thr | Gly | Ser | Val | Lys | Ile | Gly | Asp | Leu | Gly | Leu | Ala | Thr | Leu | Lys |
| | | | | 365 | | | | | 370 | | | | | 375 |
| Arg | Ala | Ser | Phe | Ala | Lys | Ser | Val | Ile | Gly | Thr | Pro | Glu | Phe | Met |
| | | | | 380 | | | | | 385 | | | | | 390 |
| Ala | Pro | Glu | Met | Tyr | Glu | Glu | Lys | Tyr | Asp | Glu | Ser | Val | Asp | Val |
| | | | | 395 | | | | | 400 | | | | | 405 |
| Tyr | Ala | Phe | Gly | Met | Cys | Met | Leu | Glu | Met | Ala | Thr | Ser | Glu | Tyr |
| | | | | 410 | | | | | 415 | | | | | 420 |
| Pro | Tyr | Ser | Glu | Cys | Gln | Asn | Ala | Ala | Gln | Ile | Tyr | Arg | Arg | Val |
| | | | | 425 | | | | | 430 | | | | | 435 |
| Thr | Ser | Gly | Val | Lys | Pro | Ala | Ser | Phe | Asp | Lys | Val | Ala | Ile | Pro |
| | | | | 440 | | | | | 445 | | | | | 450 |
| Glu | Val | Lys | Glu | Ile | Ile | Glu | Gly | Cys | Ile | Arg | Gln | Asn | Lys | Asp |
| | | | | 455 | | | | | 460 | | | | | 465 |
| Glu | Arg | Tyr | Ser | Ile | Lys | Asp | Leu | Leu | Asn | His | Ala | Phe | Phe | Gln |
| | | | | 470 | | | | | 475 | | | | | 480 |
| Glu | Glu | Thr | Gly | Val | Arg | Val | Glu | Leu | Ala | Glu | Glu | Asp | Asp | Gly |
| | | | | 485 | | | | | 490 | | | | | 495 |
| Glu | Lys | Ile | Ala | Ile | Lys | Leu | Trp | Leu | Arg | Ile | Glu | Asp | Ile | Lys |
| | | | | 500 | | | | | 505 | | | | | 510 |
| Lys | Leu | Lys | Gly | Lys | Tyr | Lys | Asp | Asn | Glu | Ala | Ile | Glu | Phe | Ser |
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| Phe | Asp | Leu | Glu | Arg | Asp | Val | Pro | Glu | Asp | Val | Ala | Gln | Glu | Met |
| | | | | 530 | | | | | 535 | | | | | 540 |
| Val | Glu | Ser | Gly | Tyr | Val | Cys | Glu | Gly | Asp | His | Lys | Thr | Met | Ala |
| | | | | 545 | | | | | 550 | | | | | 555 |
| Lys | Ala | Ile | Lys | Asp | Arg | Val | Ser | Leu | Ile | Lys | Arg | Lys | Arg | Glu |
| | | | | 560 | | | | | 565 | | | | | 570 |
| Gln | Arg | Gln | Leu | Val | Arg | Glu | Glu | Gln | Glu | Lys | Lys | Lys | Gln | Glu |
| | | | | 575 | | | | | 580 | | | | | 585 |
| Glu | Ser | Ser | Leu | Lys | Gln | Gln | Val | Glu | Gln | Ser | Ser | Ala | Ser | Gln |
| | | | | 590 | | | | | 595 | | | | | 600 |
| Thr | Gly | Ile | Lys | Gln | Leu | Pro | Ser | Ala | Ser | Thr | Gly | Ile | Pro | Thr |
| | | | </ | | | | | | | | | | | |

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|---|------|------|------|
| Ser Tyr Gly Ser Gln His Glu Gln Ala His Ser Thr Gly Thr Val | 680 | 685 | 690 |
| Pro Gly His Ile Pro Ser Thr Val Gln Ala Gln Ser Gln Pro His | 695 | 700 | 705 |
| Gly Val Tyr Pro Pro Ser Ser Val Ala Gln Gly Gln Ser Gln Gly | 710 | 715 | 720 |
| Gln Pro Ser Ser Ser Ser Leu Thr Gly Val Ser Ser Ser Gln Pro | 725 | 730 | 735 |
| Ile Gln His Pro Gln Gln Gln Gly Ile Gln Gln Thr Ala Pro Pro | 740 | 745 | 750 |
| Gln Gln Thr Val Gln Tyr Ser Leu Ser Gln Thr Ser Thr Ser Ser | 755 | 760 | 765 |
| Glu Ala Thr Thr Ala Gln Pro Val Ser Gln Pro Gln Ala Pro Gln | 770 | 775 | 780 |
| Val Leu Pro Gln Val Ser Ala Gly Lys Gln Ser Thr Gln Gly Val | 785 | 790 | 795 |
| Ser Gln Val Ala Pro Ala Glu Pro Val Ala Val Ala Gln Pro Gln | 800 | 805 | 810 |
| Ala Thr Gln Pro Thr Thr Leu Ala Ser Ser Val Asp Ser Ala His | 815 | 820 | 825 |
| Ser Asp Val Ala Ser Gly Met Ser Asp Gly Asn Glu Asn Val Pro | 830 | 835 | 840 |
| Ser Ser Ser Gly Arg His Glu Gly Arg Thr Thr Lys Arg His Tyr | 845 | 850 | 855 |
| Arg Lys Ser Val Arg Ser Arg Ser Arg His Glu Lys Thr Ser Arg | 860 | 865 | 870 |
| Pro Lys Leu Arg Ile Leu Asn Val Ser Asn Lys Gly Asp Arg Val | 875 | 880 | 885 |
| Val Glu Cys Gln Leu Glu Thr His Asn Arg Lys Met Val Thr Phe | 890 | 895 | 900 |
| Lys Phe Asp Leu Asp Gly Asp Asn Pro Glu Glu Ile Ala Thr Ile | 905 | 910 | 915 |
| Met Val Asn Asn Asp Phe Ile Leu Ala Ile Glu Arg Glu Ser Phe | 920 | 925 | 930 |
| Val Asp Gln Val Arg Glu Ile Ile Glu Lys Ala Asp Glu Met Leu | 935 | 940 | 945 |
| Ser Glu Asp Val Ser Val Glu Pro Glu Gly Asp Gln Gly Leu Glu | 950 | 955 | 960 |
| Ser Leu Gln Gly Lys Asp Asp Tyr Gly Phe Ser Gly Ser Gln Lys | 965 | 970 | 975 |
| Leu Glu Gly Glu Phe Lys Gln Pro Ile Pro Ala Ser Ser Met Pro | 980 | 985 | 990 |
| Gln Gln Ile Gly Ile Pro Thr Ser Ser Leu Thr Gln Val Val His | 995 | 1000 | 1005 |
| Ser Ala Gly Arg Arg Phe Ile Val Ser Pro Val Pro Glu Ser Arg | 1010 | 1015 | 1020 |
| Leu Arg Glu Ser Lys Val Phe Pro Ser Glu Ile Thr Asp Thr Val | 1025 | 1030 | 1035 |
| Ala Ala Ser Thr Ala Gln Ser Pro Gly Met Asn Leu Ser His Ser | 1040 | 1045 | 1050 |
| Ala Ser Ser Leu Ser Leu Gln Gln Ala Phe Ser Glu Leu Arg Arg | 1055 | 1060 | 1065 |
| Ala Gln Met Thr Glu Gly Pro Asn Thr Ala Pro Pro Asn Phe Ser | 1070 | 1075 | 1080 |
| His Thr Gly Pro Thr Phe Pro Val Val Pro Pro Phe Leu Ser Ser | 1085 | 1090 | 1095 |

| | | |
|---|------|------|
| Ile Ala Gly Val Pro Thr Thr Ala Ala Ala Thr Ala Pro Val Pro | | |
| 1100 | 1105 | 1110 |
| Ala Thr Ser Ser Pro Pro Asn Asp Ile Ser Thr Ser Val Ile Gln | | |
| 1115 | 1120 | 1125 |
| Ser Glu Val Thr Val Pro Thr Glu Glu Gly Ile Ala Gly Val Ala | | |
| 1130 | 1135 | 1140 |
| Thr Ser Thr Gly Val Val Thr Ser Gly Gly Leu Pro Ile Pro Pro | | |
| 1145 | 1150 | 1155 |
| Val Ser Glu Ser Pro Val Leu Ser Ser Val Val Ser Ser Ile Thr | | |
| 1160 | 1165 | 1170 |
| Ile Pro Ala Val Val Ser Ile Ser Thr Thr Ser Pro Ser Leu Gln | | |
| 1175 | 1180 | 1185 |
| Val Pro Thr Ser Thr Ser Glu Ile Val Val Ser Ser Thr Ala Leu | | |
| 1190 | 1195 | 1200 |
| Tyr Pro Ser Val Thr Val Ser Ala Thr Ser Ala Ser Ala Gly Gly | | |
| 1205 | 1210 | 1215 |
| Ser Thr Ala Thr Pro Gly Pro Lys Pro Pro Ala Val Val Ser Gln | | |
| 1220 | 1225 | 1230 |
| Gln Ala Ala Gly Ser Thr Thr Val Gly Ala Thr Leu Thr Ser Val | | |
| 1235 | 1240 | 1245 |
| Ser Thr Thr Thr Ser Phe Pro Ser Thr Ala Ser Gln Leu Ser Ile | | |
| 1250 | 1255 | 1260 |
| Gln Leu Ser Ser Ser Thr Ser Thr Pro Thr Leu Ala Glu Thr Val | | |
| 1265 | 1270 | 1275 |
| Val Val Ser Ala His Ser Leu Asp Lys Thr Ser His Ser Ser Thr | | |
| 1280 | 1285 | 1290 |
| Thr Gly Leu Ala Phe Ser Leu Ser Ala Pro Ser Ser Ser Ser Ser | | |
| 1295 | 1300 | 1305 |
| Pro Gly Ala Gly Val Ser Ser Tyr Ile Ser Gln Pro Gly Gly Leu | | |
| 1310 | 1315 | 1320 |
| His Pro Leu Val Ile Pro Ser Val Ile Ala Ser Thr Pro Ile Leu | | |
| 1325 | 1330 | 1335 |
| Pro Gln Ala Ala Gly Pro Thr Ser Thr Pro Leu Leu Pro Gln Val | | |
| 1340 | 1345 | 1350 |
| Pro Ser Ile Pro Pro Leu Val Gln Pro Val Ala Asn Val Pro Ala | | |
| 1355 | 1360 | 1365 |
| Val Gln Gln Thr Leu Ile His Ser Gln Pro Gln Pro Ala Leu Leu | | |
| 1370 | 1375 | 1380 |
| Pro Asn Gln Pro His Thr His Cys Pro Glu Val Asp Ser Asp Thr | | |
| 1385 | 1390 | 1395 |
| Gln Pro Lys Ala Pro Gly Ile Asp Asp Ile Lys Thr Leu Glu Glu | | |
| 1400 | 1405 | 1410 |
| Lys Leu Arg Ser Leu Phe Ser Glu His Ser Ser Ser Gly Ala Gln | | |
| 1415 | 1420 | 1425 |
| His Ala Ser Val Ser Leu Glu Thr Ser Leu Val Ile Glu Ser Thr | | |
| 1430 | 1435 | 1440 |
| Val Thr Pro Gly Ile Pro Thr Thr Ala Val Ala Pro Ser Lys Leu | | |
| 1445 | 1450 | 1455 |
| Leu Thr Ser Thr Thr Ser Thr Cys Leu Pro Pro Thr Asn Leu Pro | | |
| 1460 | 1465 | 1470 |
| Leu Gly Thr Val Ala Leu Pro Val Thr Pro Val Val Thr Pro Gly | | |
| 1475 | 1480 | 1485 |
| Gln Val Ser Thr Pro Val Ser Thr Thr Thr Ser Gly Val Lys Pro | | |
| 1490 | 1495 | 1500 |
| Gly Thr Ala Pro Ser Lys Pro Pro Leu Thr Lys Ala Pro Val Leu | | |
| 1505 | 1510 | 1515 |

| | | | |
|---|------|------|------|
| Pro Val Gly Thr Glu Leu Pro Ala Gly Thr Leu Pro Ser Glu Gln | 1520 | 1525 | 1530 |
| Leu Pro Pro Phe Pro Gly Pro Ser Leu Thr Gln Ser Gln Gln Pro | 1535 | 1540 | 1545 |
| Leu Glu Asp Leu Asp Ala Gln Leu Arg Arg Thr Leu Ser Pro Glu | 1550 | 1555 | 1560 |
| Met Ile Thr Val Thr Ser Ala Val Gly Pro Val Ser Met Ala Ala | 1565 | 1570 | 1575 |
| Pro Thr Ala Ile Thr Glu Ala Gly Thr Gln Pro Gln Lys Gly Val | 1580 | 1585 | 1590 |
| Ser Gln Val Lys Glu Gly Pro Val Leu Ala Thr Ser Ser Gly Ala | 1595 | 1600 | 1605 |
| Gly Val Phe Lys Met Gly Arg Phe Gln Val Ser Val Ala Ala Asp | 1610 | 1615 | 1620 |
| Gly Ala Gln Lys Glu Gly Lys Asn Lys Ser Glu Asp Ala Lys Ser | 1625 | 1630 | 1635 |
| Val His Phe Glu Ser Ser Thr Ser Glu Ser Ser Val Leu Ser Ser | 1640 | 1645 | 1650 |
| Ser Ser Pro Glu Ser Thr Leu Val Lys Pro Glu Pro Asn Gly Ile | 1655 | 1660 | 1665 |
| Thr Ile Pro Gly Ile Ser Ser Asp Val Pro Glu Ser Ala His Lys | 1670 | 1675 | 1680 |
| Thr Thr Ala Ser Glu Ala Lys Ser Asp Thr Gly Gln Pro Thr Lys | 1685 | 1690 | 1695 |
| Val Gly Arg Phe Gln Val Thr Thr Thr Ala Asn Lys Val Gly Arg | 1700 | 1705 | 1710 |
| Phe Ser Val Ser Lys Thr Glu Asp Lys Ile Thr Asp Thr Lys Lys | 1715 | 1720 | 1725 |
| Glu Gly Pro Val Ala Ser Pro Pro Phe Met Asp Leu Glu Gln Ala | 1730 | 1735 | 1740 |
| Val Leu Pro Ala Val Ile Pro Lys Lys Glu Lys Pro Glu Leu Ser | 1745 | 1750 | 1755 |
| Glu Pro Ser His Leu Asn Gly Pro Ser Ser Asp Pro Glu Ala Ala | 1760 | 1765 | 1770 |
| Phe Leu Ser Arg Asp Val Asp Asp Gly Ser Gly Ser Pro His Ser | 1775 | 1780 | 1785 |
| Pro His Gln Leu Ser Ser Lys Ser Leu Pro Ser Gln Asn Leu Ser | 1790 | 1795 | 1800 |
| Gln Ser Leu Ser Asn Ser Phe Asn Ser Ser Tyr Met Ser Ser Asp | 1805 | 1810 | 1815 |
| Asn Glu Ser Asp Ile Glu Asp Glu Asp Leu Lys Leu Glu Leu Arg | 1820 | 1825 | 1830 |
| Arg Leu Arg Asp Lys His Leu Lys Glu Ile Gln Asp Leu Gln Ser | 1835 | 1840 | 1845 |
| Arg Gln Lys His Glu Ile Glu Ser Leu Tyr Thr Lys Leu Gly Lys | 1850 | 1855 | 1860 |
| Val Pro Pro Ala Val Ile Ile Pro Pro Ala Ala Pro Leu Ser Gly | 1865 | 1870 | 1875 |
| Arg Arg Arg Arg Thr Lys Ser Lys Gly Ser Lys Ser Ser Arg | 1880 | 1885 | 1890 |
| Ser Ser Ser Leu Gly Asn Lys Ser Pro Gln Leu Ser Gly Asn Leu | 1895 | 1900 | 1905 |
| Ser Gly Gln Ser Ala Ala Ser Val Leu His Pro Gln Gln Thr Leu | 1910 | 1915 | 1920 |
| His Pro Pro Gly Asn Ile Pro Glu Ser Gly Gln Asn Gln Leu Leu | 1925 | 1930 | 1935 |

Gln Pro Leu Lys Pro Ser Pro Ser Ser Asp Asn Leu Tyr Ser Ala
 1940 1945 1950
 Phe Thr Ser Asp Gly Ala Ile Ser Val Pro Ser Leu Ser Ala Pro
 1955 1960 1965
 Gly Gln Gly Thr Ser Ser Thr Asn Thr Val Gly Ala Thr Val Asn
 1970 1975 1980
 Ser Gln Ala Ala Gln Ala Gln Pro Pro Ala Met Thr Ser Ser Arg
 1985 1990 1995
 Lys Gly Thr Phe Thr Asp Asp Leu His Lys Leu Val Asp Asn Trp
 2000 2005 2010
 Ala Arg Asp Ala Met Asn Leu Ser Gly Arg Arg Gly Ser Lys Gly
 2015 2020 2025
 His Met Asn Tyr Glu Gly Pro Gly Met Ala Arg Lys Phe Ser Ala
 2030 2035 2040
 Pro Gly Gln Leu Cys Ile Ser Met Thr Ser Asn Leu Gly Gly Ser
 2045 2050 2055
 Ala Pro Ile Ser Ala Ala Ser Ala Thr Ser Leu Gly His Phe Thr
 2060 2065 2070
 Lys Ser Met Cys Pro Pro Gln Gln Tyr Gly Phe Pro Ala Thr Pro
 2075 2080 2085
 Phe Gly Ala Gln Trp Ser Gly Thr Gly Gly Pro Ala Pro Gln Pro
 2090 2095 2100
 Leu Gly Gln Phe Gln Pro Val Gly Thr Ala Ser Leu Gln Asn Phe
 2105 2110 2115
 Asn Ile Ser Asn Leu Gln Lys Ser Ile Ser Asn Pro Pro Gly Ser
 2120 2125 2130
 Asn Leu Arg Thr Thr
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<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

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 Thr Thr Ala Leu Gln Lys Leu Glu Gly Phe Ala Ser Arg Leu Phe
 20 25 30
 His Arg His Ser Lys Gly Thr Ala His Asp Gln Lys Thr Ala Leu
 35 40 45
 Glu Asn Asp Ser Leu His Phe Ser Glu His Thr Ala Leu Trp Asp
 50 55 60
 Arg Ser Met Lys Glu Phe Leu Ala Lys Ala Lys Glu Asp Phe Leu
 65 70 75
 Lys Lys Trp Glu Asn Pro Thr Gln Asn Asn Ala Gly Leu Glu Asp
 80 85 90
 Phe Glu Arg Lys Lys Thr Leu Gly Thr Gly Ser Phe Gly Arg Val
 95 100 105
 Met Leu Val Lys His Lys Ala Thr Glu Gln Tyr Tyr Ala Met Lys
 110 115 120
 Ile Leu Asp Lys Gln Lys Val Val Lys Leu Lys Gln Ile Glu His

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125      130      135
Thr Leu Asn Glu Lys Arg Ile Leu Gln Ala Val Asn Phe Pro Phe
140      145      150
Leu Val Arg Leu Glu Tyr Ala Phe Lys Asp Asn Ser Asn Leu Tyr
155      160      165
Met Val Met Glu Tyr Val Pro Gly Gly Glu Met Phe Ser His Leu
170      175      180
Arg Arg Ile Gly Arg Phe Ser Glu Pro His Ala Arg Phe Tyr Ala
185      190      195
Ala Gln Ile Val Leu Thr Phe Glu Tyr Leu His Ser Leu Asp Leu
200      205      210
Ile Tyr Arg Asp Leu Lys Pro Glu Asn Leu Leu Ile Asp His Gln
215      220      225
Gly Tyr Ile Gln Val Thr Asp Phe Gly Phe Ala Lys Arg Val Lys
230      235      240
Gly Arg Thr Trp Thr Leu Cys Gly Thr Pro Glu Tyr Leu Ala Pro
245      250      255
Glu Ile Ile Leu Ser Lys Gly Tyr Asn Lys Ala Val Asp Trp Trp
260      265      270
Ala Leu Gly Val Leu Ile Tyr Glu Met Ala Ala Gly Tyr Pro Pro
275      280      285
Phe Phe Ala Asp Gln Pro Ile Gln Ile Tyr Glu Lys Ile Val Ser
290      295      300
Gly Lys Val Arg Phe Pro Ser His Phe Ser Ser Asp Leu Lys Asp
305      310      315
Leu Leu Arg Asn Leu Leu Gln Val Asp Leu Thr Lys Arg Phe Gly
320      325      330
Asn Leu Lys Asn Gly Val Ser Asp Ile Lys Thr His Lys Trp Phe
335      340      345
Ala Thr Thr Asp Trp Ile Ala Ile Tyr Gln Arg Lys Val Glu Ala
350      355      360
Pro Phe Ile Pro Lys Phe Arg Gly Ser Gly Asp Thr Ser Asn Phe
365      370      375
Asp Asp Tyr Glu Glu Glu Asp Ile Arg Val Ser Ile Thr Glu Lys
380      385      390
Cys Ala Lys Glu Phe Gly Glu Phe
395

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<210> 11

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<212> PRT

<213> Homo sapiens

<220>

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<223> Incyte ID No: 7481989CD1

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Met Glu Gly Asp Gly Val Pro Trp Gly Ser Glu Pro Val Ser Gly
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Pro Gly Pro Gly Gly Gly Gly Met Ile Arg Glu Leu Cys Arg Gly
20      25      30
Phe Gly Arg Tyr Arg Arg Tyr Leu Gly Arg Leu Arg Gln Asn Leu
35      40      45
Arg Glu Thr Gln Lys Phe Phe Arg Asp Ile Lys Cys Ser His Asn
50      55      60

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| | | | |
|---|-----|-----|-----|
| His Thr Cys Leu Ser Ser Leu Thr Gly Gly Gly Gly Ala Glu Arg | 65 | 70 | 75 |
| Gly Pro Ala Gly Asp Val Ala Glu Thr Gly Leu Gln Ala Gly Gln | 80 | 85 | 90 |
| Leu Ser Cys Ile Ser Phe Pro Pro Lys Glu Glu Lys Tyr Leu Gln | 95 | 100 | 105 |
| Gln Ile Val Asp Cys Leu Pro Cys Ile Leu Ile Leu Gly Gln Asp | 110 | 115 | 120 |
| Cys Asn Val Lys Cys Gln Leu Leu Asn Leu Leu Leu Gly Val Gln | 125 | 130 | 135 |
| Val Leu Pro Thr Thr Lys Leu Gly Ser Glu Glu Ser Cys Lys Leu | 140 | 145 | 150 |
| Arg Arg Leu Arg Phe Thr Tyr Gly Thr Gln Thr Arg Val Ser Leu | 155 | 160 | 165 |
| Ala Leu Pro Gly Gln Tyr Glu Leu Val His Thr Leu Val Ala His | 170 | 175 | 180 |
| Gln Gly Asn Trp Glu Thr Ile Pro Glu Glu Asp Leu Glu Val Gln | 185 | 190 | 195 |
| Glu Asn Asn Glu Asp Ala Ala His Val Leu Ala Glu Leu Glu Val | 200 | 205 | 210 |
| Thr Met His His Ala Leu Leu Gln Glu Val Asp Val Val Val Ala | 215 | 220 | 225 |
| Pro Cys Gln Gly Leu Arg Pro Thr Val Asp Val Leu Gly Asp Leu | 230 | 235 | 240 |
| Val Asn Asp Phe Leu Pro Val Ile Thr Tyr Ala Leu His Lys Asp | 245 | 250 | 255 |
| Glu Leu Ser Glu Arg Asp Glu Gln Glu Leu Gln Glu Ile Arg Lys | 260 | 265 | 270 |
| Tyr Phe Ser Phe Pro Val Phe Phe Phe Lys Val Pro Lys Leu Gly | 275 | 280 | 285 |
| Ser Glu Ile Ile Asp Ser Ser Thr Arg Arg Met Glu Ser Glu Arg | 290 | 295 | 300 |
| Ser Pro Leu Tyr Arg Gln Leu Ile Asp Leu Gly Tyr Leu Ser Ser | 305 | 310 | 315 |
| Ser His Trp Asn Cys Gly Ala Pro Gly Gln Asp Thr Lys Ala Gln | 320 | 325 | 330 |
| Ser Met Leu Val Glu Gln Ser Glu Lys Leu Arg His Leu Ser Thr | 335 | 340 | 345 |
| Phe Ser His Gln Val Leu Gln Thr Arg Leu Val Asp Ala Ala Lys | 350 | 355 | 360 |
| Ala Leu Asn Leu Val His Cys His Cys Leu Asp Ile Phe Ile Asn | 365 | 370 | 375 |
| Gln Ala Phe Asp Met Gln Arg Asp Leu Gln Ile Thr Pro Lys Arg | 380 | 385 | 390 |
| Leu Glu Tyr Thr Arg Lys Lys Glu Asn Glu Leu Tyr Glu Ser Leu | 395 | 400 | 405 |
| Met Asn Ile Ala Asn Arg Lys Gln Glu Glu Met Lys Asp Met Ile | 410 | 415 | 420 |
| Val Glu Thr Leu Asn Thr Met Lys Glu Glu Leu Leu Asp Asp Ala | 425 | 430 | 435 |
| Thr Asn Met Glu Phe Lys Asp Val Ile Val Pro Glu Asn Gly Glu | 440 | 445 | 450 |
| Pro Val Gly Thr Arg Glu Ile Lys Cys Cys Ile Arg Gln Ile Gln | 455 | 460 | 465 |
| Glu Leu Ile Ile Ser Arg Leu Asn Gln Ala Val Ala Asn Lys Leu | 470 | 475 | 480 |

| | | |
|-----------------|---|---------|
| Ile Ser Ser Val | Asp Tyr Leu Arg Glu Ser Phe Val Gly Thr Leu | |
| | 485 | 490 495 |
| Glu Arg Cys Leu | Gln Ser Leu Glu Lys Ser Gln Asp Val Ser Val | |
| | 500 | 505 510 |
| His Ile Thr Ser | Asn Tyr Leu Lys Gln Ile Leu Asn Ala Ala Tyr | |
| | 515 | 520 525 |
| His Val Glu Val | Thr Phe His Ser Gly Ser Ser Val Thr Arg Met | |
| | 530 | 535 540 |
| Leu Trp Glu Gln | Ile Lys Gln Ile Ile Gln Arg Ile Thr Trp Val | |
| | 545 | 550 555 |
| Ser Pro Pro Ala | Ile Thr Leu Glu Trp Lys Arg Lys Val Ala Gln | |
| | 560 | 565 570 |
| Glu Ala Ile Glu | Ser Leu Ser Ala Ser Lys Leu Ala Lys Ser Ile | |
| | 575 | 580 585 |
| Cys Ser Gln Phe | Arg Thr Arg Leu Asn Ser Ser His Glu Ala Phe | |
| | 590 | 595 600 |
| Ala Ala Ser Leu | Arg Gln Leu Glu Ala Gly His Ser Gly Arg Leu | |
| | 605 | 610 615 |
| Glu Lys Thr Glu | Asp Leu Trp Leu Arg Val Arg Lys Asp His Ala | |
| | 620 | 625 630 |
| Pro Arg Leu Ala | Arg Leu Ser Leu Glu Ser Arg Ser Leu Gln Asp | |
| | 635 | 640 645 |
| Val Leu Leu His | Arg Lys Pro Lys Leu Gly Gln Glu Leu Gly Arg | |
| | 650 | 655 660 |
| Gly Gln Tyr Gly | Val Val Tyr Leu Cys Asp Asn Trp Gly Gly His | |
| | 665 | 670 675 |
| Phe Pro Cys Ala | Leu Lys Ser Val Val Pro Pro Asp Glu Lys His | |
| | 680 | 685 690 |
| Trp Asn Asp Leu | Ala Leu Glu Phe His Tyr Met Arg Ser Leu Pro | |
| | 695 | 700 705 |
| Lys His Glu Arg | Leu Val Asp Leu His Gly Ser Val Ile Asp Tyr | |
| | 710 | 715 720 |
| Asn Tyr Gly Gly | Gly Ser Ser Ile Ala Val Leu Leu Ile Met Glu | |
| | 725 | 730 735 |
| Arg Leu His Arg | Asp Leu Tyr Thr Gly Leu Lys Ala Gly Leu Thr | |
| | 740 | 745 750 |
| Leu Glu Thr Arg | Leu Gln Ile Ala Leu Asp Val Val Glu Gly Ile | |
| | 755 | 760 765 |
| Arg Phe Leu His | Ser Gln Gly Leu Val His Arg Asp Ile Lys Leu | |
| | 770 | 775 780 |
| Lys Asn Val Leu | Leu Asp Lys Gln Asn Arg Ala Lys Ile Thr Asp | |
| | 785 | 790 795 |
| Leu Gly Phe Cys | Lys Pro Glu Ala Met Met Ser Gly Ser Ile Val | |
| | 800 | 805 810 |
| Gly Thr Pro Ile | His Met Ala Pro Glu Leu Phe Thr Gly Lys Tyr | |
| | 815 | 820 825 |
| Asp Asn Ser Val | Asp Val Tyr Ala Phe Gly Ile Leu Phe Trp Tyr | |
| | 830 | 835 840 |
| Ile Cys Ser Gly | Ser Val Lys Leu Pro Glu Ala Phe Glu Arg Cys | |
| | 845 | 850 855 |
| Ala Ser Lys Asp | His Leu Trp Asn Asn Val Arg Arg Gly Ala Arg | |
| | 860 | 865 870 |
| Pro Glu Arg Leu | Pro Val Phe Asp Glu Glu Cys Trp Gln Leu Met | |
| | 875 | 880 885 |
| Glu Ala Cys Trp | Asp Gly Asp Pro Leu Lys Arg Pro Leu Leu Gly | |
| | 890 | 895 900 |

Ile Val Gln Pro Met Leu Gln Gly Ile Met Asn Arg Leu Cys Lys
 905 910 915
 Ser Asn Ser Glu Gln Pro Asn Arg Gly Leu Asp Asp Ser Thr
 920 925

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 <212> PRT
 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 55052990CD1

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 Ala Ala Ala Pro Pro Gly Glu Asp Gly Ala Gly Ala Gly Ala Glu
 20 25 30
 Glu Glu Glu Glu Glu Glu Glu Ala Ala Ala Val Gly Pro
 35 40 45
 Gly Glu Leu Gly Cys Asp Ala Pro Leu Pro Tyr Trp Thr Ala Val
 50 55 60
 Phe Glu Tyr Glu Ala Ala Gly Glu Asp Glu Leu Thr Leu Arg Leu
 65 70 75
 Gly Asp Val Val Glu Val Leu Ser Lys Asp Ser Gln Val Ser Gly
 80 85 90
 Asp Glu Gly Trp Trp Thr Gly Gln Leu Asn Gln Arg Val Gly Ile
 95 100 105
 Phe Pro Ser Asn Tyr Val Thr Pro Arg Ser Ala Phe Ser Ser Arg
 110 115 120
 Cys Gln Pro Gly Gly Glu Asp Pro Ser Cys Tyr Pro Pro Ile Gln
 125 130 135
 Leu Leu Glu Ile Asp Phe Ala Glu Leu Thr Leu Glu Glu Ile Ile
 140 145 150
 Gly Ile Gly Gly Phe Gly Lys Val Tyr Arg Ala Phe Trp Ile Gly
 155 160 165
 Asp Glu Val Ala Val Lys Ala Ala Arg His Asp Pro Asp Glu Asp
 170 175 180
 Ile Ser Gln Thr Ile Glu Asn Val Arg Gln Glu Ala Lys Leu Phe
 185 190 195
 Ala Met Leu Lys His Pro Asn Ile Ile Ala Leu Arg Gly Val Cys
 200 205 210
 Leu Lys Glu Pro Asn Leu Cys Leu Val Met Glu Phe Ala Arg Gly
 215 220 225
 Gly Pro Leu Asn Arg Val Leu Ser Gly Lys Arg Ile Pro Pro Asp
 230 235 240
 Ile Leu Val Asn Trp Ala Val Gln Ile Ala Arg Gly Met Asn Tyr
 245 250 255
 Leu Leu Asp Glu Ala Ile Val Pro Ile Ile His Arg Asp Leu Lys
 260 265 270
 Ser Ser Asn Ile Leu Ile Leu Gln Lys Val Glu Asn Gly Asp Leu
 275 280 285
 Ser Asn Lys Ile Leu Lys Ile Thr Asp Phe Gly Leu Ala Arg Glu
 290 295 300
 Trp His Arg Thr Thr Lys Met Ser Ala Ala Gly Thr Tyr Ala Trp

| | | | | |
|-------------------------------------|-----|-------------------------|-----|-----|
| Met Ala Pro Glu Val Ile Arg Ala Ser | 305 | Met Phe Ser Lys Gly Ser | 310 | 315 |
| Asp Val Trp Ser Tyr Gly Val Leu Leu | 320 | Trp Glu Leu Leu Thr Gly | 325 | 330 |
| Glu Val Pro Phe Arg Gly Ile Asp Gly | 335 | Leu Ala Val Ala Tyr Gly | 340 | 345 |
| Val Ala Met Asn Lys Leu Ala Leu Pro | 350 | Ile Pro Ser Thr Cys Pro | 355 | 360 |
| Glu Pro Phe Ala Lys Leu Met Glu Asp | 365 | Cys Trp Asn Pro Asp Pro | 370 | 375 |
| His Ser Arg Pro Ser Phe Thr Asn Ile | 380 | Leu Asp Gln Leu Thr Thr | 385 | 390 |
| Ile Glu Glu Ser Gly Phe Phe Glu Met | 395 | Pro Lys Asp Ser Phe His | 400 | 405 |
| Cys Leu Gln Asp Asn Trp Lys His Glu | 410 | Ile Gln Glu Met Phe Asp | 415 | 420 |
| Gln Leu Arg Ala Lys Glu Lys Glu Leu | 425 | Arg Thr Trp Glu Glu Glu | 430 | 435 |
| Leu Thr Arg Ala Ala Leu Gln Gln Lys | 440 | Asn Gln Glu Glu Leu Leu | 445 | 450 |
| Arg Arg Arg Glu Gln Glu Leu Ala Glu | 455 | Arg Glu Ile Asp Ile Leu | 460 | 465 |
| Glu Arg Glu Leu Asn Ile Ile Ile His | 470 | Gln Leu Cys Gln Glu Lys | 475 | 480 |
| Pro Arg Val Lys Lys Arg Lys Gly Lys | 485 | Phe Arg Lys Ser Arg Leu | 490 | 495 |
| Lys Leu Lys Asp Gly Asn Arg Ile Ser | 500 | Leu Pro Ser Asp Phe Gln | 505 | 510 |
| His Lys Phe Thr Val Gln Ala Ser Pro | 515 | Thr Met Asp Lys Arg Lys | 520 | 525 |
| Ser Leu Ile Asn Ser Arg Ser Ser Pro | 530 | Pro Ala Ser Pro Thr Ile | 535 | 540 |
| Ile Pro Arg Leu Arg Ala Ile Gln Leu | 545 | Thr Pro Gly Glu Ser Ser | 550 | 555 |
| Lys Thr Trp Gly Arg Ser Ser Val Val | 560 | Pro Lys Glu Glu Gly Glu | 565 | 570 |
| Glu Glu Glu Lys Arg Ala Pro Lys Lys | 575 | Gly Arg Thr Trp Gly | 580 | 585 |
| Pro Gly Thr Leu Gly Gln Lys Glu Leu | 590 | Ala Ser Gly Asp Glu Gly | 595 | 600 |
| Leu Lys Ser Leu Val Asp Gly Tyr Lys | 605 | Gln Trp Ser Ser Ser Ala | 610 | 615 |
| Pro Asn Leu Val Lys Gly Pro Arg Ser | 620 | Ser Pro Ala Leu Pro Gly | 625 | 630 |
| Phe Thr Ser Leu Met Glu Met Glu Asp | 635 | Glu Asp Ser Glu Gly Pro | 640 | 645 |
| Gly Ser Gly Glu Ser Arg Leu Gln His | 650 | Ser Pro Ser Gln Ser Tyr | 655 | 660 |
| Leu Cys Ile Pro Phe Pro Arg Gly Glu | 665 | Asp Gly Asp Gly Pro Ser | 670 | 675 |
| Ser Asp Gly Ile His Glu Glu Pro Thr | 680 | Pro Val Asn Ser Ala Thr | 685 | 690 |
| Ser Thr Pro Gln Leu Thr Pro Thr Asn | 695 | Ser Leu Lys Arg Gly Gly | 700 | 705 |
| Ala His His Arg Arg Cys Glu Val Ala | 710 | Leu Leu Gly Cys Gly Ala | 715 | 720 |

| | | | | | |
|---|------|--|------|--|------|
| | 725 | | 730 | | 735 |
| Val Leu Ala Ala Thr Gly Leu Gly Phe Asp Leu Leu Glu Ala Gly | | | | | |
| | 740 | | 745 | | 750 |
| Lys Cys Gln Leu Leu Pro Leu Glu Glu Pro Glu Pro Pro Ala Arg | | | | | |
| | 755 | | 760 | | 765 |
| Glu Glu Lys Lys Arg Arg Glu Gly Leu Phe Gln Arg Ser Ser Arg | | | | | |
| | 770 | | 775 | | 780 |
| Pro Arg Arg Ser Thr Ser Pro Pro Ser Arg Lys Leu Phe Lys Lys | | | | | |
| | 785 | | 790 | | 795 |
| Glu Glu Pro Met Leu Leu Leu Gly Asp Pro Ser Ala Ser Leu Thr | | | | | |
| | 800 | | 805 | | 810 |
| Leu Leu Ser Leu Ser Ser Ile Ser Glu Cys Asn Ser Thr Arg Ser | | | | | |
| | 815 | | 820 | | 825 |
| Leu Leu Arg Ser Asp Ser Asp Glu Ile Val Val Tyr Glu Met Pro | | | | | |
| | 830 | | 835 | | 840 |
| Val Ser Pro Val Glu Ala Pro Pro Leu Ser Pro Cys Thr His Asn | | | | | |
| | 845 | | 850 | | 855 |
| Pro Leu Val Asn Val Arg Val Glu Arg Phe Lys Arg Asp Pro Asn | | | | | |
| | 860 | | 865 | | 870 |
| Gln Ser Leu Thr Pro Thr His Val Thr Leu Thr Thr Pro Ser Gln | | | | | |
| | 875 | | 880 | | 885 |
| Pro Ser Ser His Arg Arg Thr Pro Ser Asp Gly Ala Leu Lys Pro | | | | | |
| | 890 | | 895 | | 900 |
| Glu Thr Leu Leu Ala Ser Arg Ser Pro Ser Ser Asn Gly Leu Ser | | | | | |
| | 905 | | 910 | | 915 |
| Pro Ser Pro Gly Ala Gly Glu Ser Ser Ser Ser Phe Leu Phe Pro | | | | | |
| | 920 | | 925 | | 930 |
| Phe Phe Val Pro Pro Gln Gly Met Leu Lys Thr Pro Ser Pro Ser | | | | | |
| | 935 | | 940 | | 945 |
| Arg Asp Pro Gly Glu Phe Pro Arg Leu Pro Asp Pro Asn Val Val | | | | | |
| | 950 | | 955 | | 960 |
| Phe Pro Pro Thr Pro Arg Arg Trp Asn Thr Gln Gln Asp Ser Thr | | | | | |
| | 965 | | 970 | | 975 |
| Leu Glu Arg Pro Lys Thr Leu Glu Phe Leu Pro Arg Pro Arg Pro | | | | | |
| | 980 | | 985 | | 990 |
| Ser Ala Asn Arg Gln Arg Leu Asp Pro Trp Trp Phe Val Ser Pro | | | | | |
| | 995 | | 1000 | | 1005 |
| Ser His Ala Arg Ser Thr Ser Pro Ala Asn Ser Ser Ser Thr Glu | | | | | |
| | 1010 | | 1015 | | 1020 |
| Thr Pro Ser Asn Leu Asp Ser Cys Phe Ala Ser Ser Ser Ser Thr | | | | | |
| | 1025 | | 1030 | | 1035 |
| Val Glu Glu Arg Pro Gly Leu Pro Ala Leu Leu Pro Phe Gln Ala | | | | | |
| | 1040 | | 1045 | | 1050 |
| Gly Pro Leu Pro Pro Thr Glu Arg Thr Leu Leu Asp Leu Asp Ala | | | | | |
| | 1055 | | 1060 | | 1065 |
| Glu Gly Gln Ser Gln Asp Ser Thr Val Pro Leu Cys Arg Ala Glu | | | | | |
| | 1070 | | 1075 | | 1080 |
| Leu Asn Thr His Arg Pro Ala Pro Tyr Glu Ile Gln Gln Glu Phe | | | | | |
| | 1085 | | 1090 | | 1095 |
| Trp Ser | | | | | |

<210> 13

<211> 928

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7482377CD1

<400> 13

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Met Ala Val Arg Phe Gln Val Ala Asp Met Glu Glu Leu Thr Ile
 1          5          10          15
Trp Glu Gln His Thr Ala Thr Leu Ser Lys Asp Pro Arg Arg Gly
 20          25          30
Phe Gly Ile Ala Ile Ser Gly Gly Arg Asp Arg Pro Gly Gly Ser
 35          40          45
Met Val Val Ser Asp Val Val Pro Gly Gly Pro Ala Glu Gly Arg
 50          55          60
Leu Gln Thr Gly Asp His Ile Val Met Val Asn Gly Val Ser Met
 65          70          75
Glu Asn Ala Thr Ser Ala Phe Ala Ile Gln Ile Leu Lys Thr Cys
 80          85          90
Thr Lys Met Ala Asn Ile Thr Val Lys Arg Pro Arg Arg Ile His
 95          100         105
Leu Pro Ala Thr Lys Ala Ser Pro Ser Ser Pro Gly Arg Gln Asp
 110         115         120
Ser Asp Glu Asp Asp Gly Pro Gln Arg Val Glu Glu Val Asp Gln
 125         130         135
Gly Arg Gly Tyr Asp Gly Asp Ser Ser Ser Gly Ser Gly Arg Ser
 140         145         150
Trp Asp Glu Arg Ser Arg Arg Pro Arg Pro Gly Arg Arg Gly Arg
 155         160         165
Ala Gly Ser His Gly Arg Arg Ser Pro Gly Gly Gly Ser Glu Ala
 170         175         180
Asn Gly Leu Ala Leu Val Ser Gly Phe Lys Arg Leu Pro Arg Gln
 185         190         195
Asp Val Gln Met Lys Pro Val Lys Ser Val Leu Val Lys Arg Arg
 200         205         210
Asp Ser Glu Glu Phe Gly Val Lys Leu Gly Ser Gln Ile Phe Ile
 215         220         225
Lys His Ile Thr Asp Ser Gly Leu Ala Ala Arg His Arg Gly Leu
 230         235         240
Gln Glu Gly Asp Leu Ile Leu Gln Ile Asn Gly Val Ser Ser Gln
 245         250         255
Asn Leu Ser Leu Asn Asp Thr Arg Arg Leu Ile Glu Lys Ser Glu
 260         265         270
Gly Lys Leu Ser Leu Leu Val Leu Arg Asp Arg Gly Gln Phe Leu
 275         280         285
Val Asn Ile Pro Pro Ala Val Ser Asp Ser Asp Ser Ser Pro Leu
 290         295         300
Glu Asp Ile Ser Asp Leu Ala Ser Glu Leu Ser Gln Ala Pro Pro
 305         310         315
Ser His Ile Pro Pro Pro Pro Arg His Ala Gln Arg Ser Pro Glu
 320         325         330
Ala Ser Gln Thr Asp Ser Pro Val Glu Ser Pro Arg Leu Arg Arg
 335         340         345
Glu Ser Ser Val Asp Ser Arg Thr Ile Ser Glu Pro Asp Glu Gln
 350         355         360
Arg Ser Glu Leu Pro Arg Glu Ser Ser Tyr Asp Ile Tyr Arg Val
 365         370         375
Pro Ser Ser Gln Ser Met Glu Asp Arg Gly Tyr Ser Pro Asp Thr

```

| | | | | | |
|-----------------|---------------------|---------------------|-----|--|-----|
| | 380 | | 385 | | 390 |
| Arg Val Val Arg | Phe Leu Lys Gly Lys | Ser Ile Gly Leu Arg | Leu | | |
| | 395 | | 400 | | 405 |
| Ala Gly Gly Asn | Asp Val Gly Ile Phe | Val Ser Gly Val Gln | Ala | | |
| | 410 | | 415 | | 420 |
| Gly Ser Pro Ala | Asp Gly Gln Gly Ile | Gln Glu Gly Asp Gln | Ile | | |
| | 425 | | 430 | | 435 |
| Leu Gln Val Asn | Asp Val Pro Phe Gln | Asn Leu Thr Arg Glu | Glu | | |
| | 440 | | 445 | | 450 |
| Ala Val Gln Phe | Leu Leu Gly Leu Pro | Pro Gly Glu Glu Met | Glu | | |
| | 455 | | 460 | | 465 |
| Leu Val Thr Gln | Arg Lys Gln Asp Ile | Phe Trp Lys Met Val | Gln | | |
| | 470 | | 475 | | 480 |
| Ser Arg Val Gly | Asp Ser Phe Tyr Ile | Arg Thr His Phe Glu | Leu | | |
| | 485 | | 490 | | 495 |
| Glu Pro Ser Pro | Pro Ser Gly Leu Gly | Phe Thr Arg Gly Asp | Val | | |
| | 500 | | 505 | | 510 |
| Phe His Val Leu | Asp Thr Leu His Pro | Gly Pro Gly Gln Ser | His | | |
| | 515 | | 520 | | 525 |
| Ala Arg Gly Gly | His Trp Leu Ala Val | Arg Met Gly Arg Asp | Leu | | |
| | 530 | | 535 | | 540 |
| Arg Glu Gln Glu | Arg Gly Ile Ile Pro | Asn Gln Ser Arg Ala | Glu | | |
| | 545 | | 550 | | 555 |
| Gln Leu Ala Ser | Leu Glu Ala Ala Gln | Arg Ala Val Gly Val | Gly | | |
| | 560 | | 565 | | 570 |
| Pro Gly Ser Ser | Ala Gly Ser Asn Ala | Arg Ala Glu Phe Trp | Arg | | |
| | 575 | | 580 | | 585 |
| Leu Arg Gly Leu | Arg Arg Gly Ala Lys | Lys Thr Thr Gln Arg | Ser | | |
| | 590 | | 595 | | 600 |
| Arg Glu Asp Leu | Ser Ala Leu Thr Arg | Gln Gly Arg Tyr Pro | Pro | | |
| | 605 | | 610 | | 615 |
| Tyr Glu Arg Val | Val Leu Arg Glu Ala | Ser Phe Lys Arg Pro | Val | | |
| | 620 | | 625 | | 630 |
| Val Ile Leu Gly | Pro Val Ala Asp Ile | Ala Met Gln Lys Leu | Thr | | |
| | 635 | | 640 | | 645 |
| Ala Glu Met Pro | Asp Gln Phe Glu Ile | Ala Glu Thr Val Ser | Arg | | |
| | 650 | | 655 | | 660 |
| Thr Asp Ser Pro | Ser Lys Ile Ile Lys | Leu Asp Thr Val Arg | Val | | |
| | 665 | | 670 | | 675 |
| Ile Ala Glu Lys | Asp Lys His Ala Leu | Leu Asp Val Thr Pro | Ser | | |
| | 680 | | 685 | | 690 |
| Ala Ile Glu Arg | Leu Asn Tyr Val Gln | Tyr Tyr Pro Ile Val | Val | | |
| | 695 | | 700 | | 705 |
| Phe Phe Ile Pro | Glu Ser Arg Pro Ala | Leu Lys Ala Leu Arg | Gln | | |
| | 710 | | 715 | | 720 |
| Trp Leu Ala Pro | Ala Ser Arg Arg Ser | Thr Arg Arg Leu Tyr | Ala | | |
| | 725 | | 730 | | 735 |
| Gln Ala Gln Lys | Leu Arg Lys His Ser | Ser His Leu Phe Thr | Ala | | |
| | 740 | | 745 | | 750 |
| Thr Ile Pro Leu | Asn Gly Thr Ser Asp | Thr Trp Tyr Gln Glu | Leu | | |
| | 755 | | 760 | | 765 |
| Lys Ala Ile Ile | Arg Glu Gln Gln Thr | Arg Pro Ile Trp Thr | Ala | | |
| | 770 | | 775 | | 780 |
| Glu Asp Gln Leu | Asp Gly Ser Leu Glu | Asp Asn Leu Asp Leu | Pro | | |
| | 785 | | 790 | | 795 |
| His His Gly Leu | Ala Asp Ser Ser Ala | Asp Leu Ser Cys Asp | Ser | | |

| | | | | | |
|---|-----|--|-----|--|-----|
| | 800 | | 805 | | 810 |
| Arg Val Asn Ser Asp Tyr Glu Thr Asp Gly Glu Gly Gly Ala Tyr | | | | | |
| | 815 | | 820 | | 825 |
| Thr Asp Gly Glu Gly Tyr Thr Asp Gly Glu Gly Gly Pro Tyr Thr | | | | | |
| | 830 | | 835 | | 840 |
| Asp Val Asp Asp Glu Pro Pro Ala Pro Ala Leu Ala Arg Ser Ser | | | | | |
| | 845 | | 850 | | 855 |
| Glu Pro Val Gln Ala Asp Glu Ser Gln Ser Pro Arg Asp Arg Gly | | | | | |
| | 860 | | 865 | | 870 |
| Arg Ile Ser Ala His Gln Gly Ala Gln Val Asp Ser Arg His Pro | | | | | |
| | 875 | | 880 | | 885 |
| Gln Gly Gln Trp Arg Gln Asp Ser Met Arg Thr Tyr Glu Arg Glu | | | | | |
| | 890 | | 895 | | 900 |
| Ala Leu Lys Lys Lys Phe Met Arg Val His Asp Ala Glu Ser Ser | | | | | |
| | 905 | | 910 | | 915 |
| Asp Glu Asp Gly Tyr Asp Trp Gly Pro Ala Thr Asp Leu | | | | | |
| | 920 | | 925 | | |

<210> 14

<211> 766

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7758364CD1

<400> 14

| | | |
|---|-----|-----|
| Met Ala Ser Thr Arg Ser Ile Glu Leu Glu His Phe Glu Glu Arg | | |
| 1 | 5 | 10 |
| Asp Lys Arg Pro Arg Pro Gly Ser Arg Arg Gly Ala Pro Ser Ser | | |
| | 20 | 25 |
| Ser Gly Gly Ser Ser Ser Ser Gly Pro Lys Gly Asn Gly Leu Ile | | |
| | 35 | 40 |
| Pro Ser Pro Ala His Ser Ala His Cys Ser Phe Tyr Arg Thr Arg | | |
| | 50 | 55 |
| Thr Leu Gln Ala Leu Ser Ser Glu Lys Lys Ala Lys Lys Ala Arg | | |
| | 65 | 70 |
| Phe Tyr Arg Asn Gly Asp Arg Tyr Phe Lys Gly Leu Val Phe Ala | | |
| | 80 | 85 |
| Ile Ser Ser Asp Arg Phe Arg Ser Phe Asp Ala Leu Leu Ile Glu | | |
| | 95 | 100 |
| Leu Thr Arg Ser Leu Ser Asp Asn Val Asn Leu Pro Gln Gly Val | | |
| | 110 | 115 |
| Arg Thr Ile Tyr Thr Ile Asp Gly Ser Arg Lys Val Thr Ser Leu | | |
| | 125 | 130 |
| Asp Glu Leu Leu Glu Gly Glu Ser Tyr Val Cys Ala Ser Asn Glu | | |
| | 140 | 145 |
| Pro Phe Arg Lys Val Asp Tyr Thr Lys Asn Ile Asn Pro Asn Trp | | |
| | 155 | 160 |
| Ser Val Asn Ile Lys Gly Gly Thr Ser Arg Ala Leu Ala Ala Ala | | |
| | 170 | 175 |
| Ser Ser Val Lys Ser Glu Val Lys Glu Ser Lys Asp Phe Ile Lys | | |
| | 185 | 190 |
| Pro Lys Leu Val Thr Val Ile Arg Ser Gly Val Lys Pro Arg Lys | | |
| | 200 | 205 |
| | | 210 |

| | | | |
|-----------------|---------------------|---------------------|-----|
| Ala Val Arg Ile | Leu Leu Asn Lys Lys | Thr Ala His Ser Phe | Glu |
| 215 | 220 | | 225 |
| Gln Val Leu Thr | Asp Ile Thr Glu Ala | Ile Lys Leu Asp Ser | Gly |
| 230 | 235 | | 240 |
| Val Val Lys Arg | Leu Cys Thr Leu Asp | Gly Lys Gln Val Thr | Cys |
| 245 | 250 | | 255 |
| Leu Gln Asp Phe | Phe Gly Asp Asp Asp | Val Phe Ile Ala Cys | Gly |
| 260 | 265 | | 270 |
| Pro Glu Lys Phe | Arg Tyr Ala Gln Asp | Asp Phe Val Leu Asp | His |
| 275 | 280 | | 285 |
| Ser Glu Cys Arg | Val Leu Lys Ser Ser | Tyr Ser Arg Ser Ser | Ala |
| 290 | 295 | | 300 |
| Val Lys Tyr Ser | Gly Ser Lys Ser Pro | Gly Pro Ser Arg Arg | Ser |
| 305 | 310 | | 315 |
| Lys Ser Pro Ala | Ser Val Asn Gly Thr | Pro Ser Ser Gln Leu | Ser |
| 320 | 325 | | 330 |
| Thr Pro Lys Ser | Thr Lys Ser Ser Ser | Ser Ser Pro Thr Ser | Pro |
| 335 | 340 | | 345 |
| Gly Ser Phe Arg | Gly Leu Lys Gln Ile | Ser Ala His Gly Arg | Ser |
| 350 | 355 | | 360 |
| Ser Ser Asn Val | Asn Gly Gly Pro Glu | Leu Asp Arg Cys Ile | Ser |
| 365 | 370 | | 375 |
| Pro Glu Gly Val | Asn Gly Asn Arg Cys | Ser Glu Ser Ser Thr | Leu |
| 380 | 385 | | 390 |
| Leu Glu Lys Tyr | Lys Ile Gly Lys Val | Ile Gly Asp Gly Asn | Phe |
| 395 | 400 | | 405 |
| Ala Val Val Lys | Glu Cys Ile Asp Arg | Ser Thr Gly Lys Glu | Phe |
| 410 | 415 | | 420 |
| Ala Leu Lys Ile | Ile Asp Lys Ala Lys | Cys Cys Gly Lys Glu | His |
| 425 | 430 | | 435 |
| Leu Ile Glu Asn | Glu Val Ser Ile Leu | Arg Arg Val Lys His | Pro |
| 440 | 445 | | 450 |
| Asn Ile Ile Met | Leu Val Glu Glu Met | Glu Thr Ala Thr Glu | Leu |
| 455 | 460 | | 465 |
| Phe Leu Val Met | Glu Leu Val Lys Gly | Gly Asp Leu Phe Asp | Ala |
| 470 | 475 | | 480 |
| Ile Thr Ser Ser | Thr Lys Tyr Thr Glu | Arg Asp Gly Ser Ala | Met |
| 485 | 490 | | 495 |
| Val Tyr Asn Leu | Ala Asn Ala Leu Arg | Tyr Leu His Gly Leu | Ser |
| 500 | 505 | | 510 |
| Ile Val His Arg | Asp Ile Lys Pro Glu | Asn Leu Leu Val Cys | Glu |
| 515 | 520 | | 525 |
| Tyr Pro Asp Gly | Thr Lys Ser Leu Lys | Leu Gly Asp Phe Gly | Leu |
| 530 | 535 | | 540 |
| Ala Thr Val Val | Glu Gly Pro Leu Tyr | Thr Val Cys Gly Thr | Pro |
| 545 | 550 | | 555 |
| Thr Tyr Val Ala | Pro Glu Ile Ile Ala | Glu Thr Gly Tyr Gly | Leu |
| 560 | 565 | | 570 |
| Lys Val Asp Ile | Trp Ala Ala Gly Val | Ile Thr Tyr Ile Leu | Leu |
| 575 | 580 | | 585 |
| Cys Gly Phe Pro | Pro Phe Arg Ser Glu | Asn Asn Leu Gln Glu | Asp |
| 590 | 595 | | 600 |
| Leu Phe Asp Gln | Ile Leu Ala Gly Lys | Leu Glu Phe Pro Ala | Pro |
| 605 | 610 | | 615 |
| Tyr Trp Asp Asn | Ile Thr Asp Ser Ala | Lys Glu Leu Ile Ser | Gln |
| 620 | 625 | | 630 |

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Met Leu Gln Val Asn Val Glu Ala Arg Cys Thr Ala Gly Gln Ile
      635                      640                      645
Leu Ser His Pro Trp Val Ser Asp Asp Ala Ser Gln Glu Asn Asn
      650                      655                      660
Met Gln Ala Glu Val Thr Gly Lys Leu Lys Gln His Phe Asn Asn
      665                      670                      675
Ala Leu Pro Lys Gln Asn Ser Thr Thr Thr Gly Val Ser Val Ile
      680                      685                      690
Met Asn Thr Ala Leu Asp Lys Glu Gly Gln Ile Phe Cys Ser Lys
      695                      700                      705
His Cys Gln Asp Ser Gly Arg Pro Gly Met Glu Pro Ile Ser Pro
      710                      715                      720
Val Pro Pro Ser Val Glu Glu Ile Pro Val Pro Gly Glu Ala Val
      725                      730                      735
Pro Ala Pro Thr Pro Pro Glu Ser Pro Thr Pro His Cys Pro Pro
      740                      745                      750
Ala Ala Pro Gly Gly Glu Arg Ala Gly Thr Trp Arg Arg His Arg
      755                      760                      765
Asp

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<210> 15

<211> 447

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5850001CD1

<400> 15

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Met Gly Ala Gly Arg Leu Gly Ala Pro Met Glu Arg His Gly Arg
  1                      5                      10                      15
Ala Ser Ala Thr Ser Val Ser Ser Ala Gly Glu Gln Ala Ala Gly
      20                      25                      30
Asp Pro Glu Gly Arg Arg Gln Glu Pro Leu Arg Arg Arg Ala Ser
      35                      40                      45
Ser Ala Ser Val Pro Ala Val Gly Ala Ser Ala Glu Gly Thr Arg
      50                      55                      60
Arg Asp Arg Leu Gly Ser Tyr Ser Gly Pro Thr Ser Val Ser Arg
      65                      70                      75
Gln Arg Val Glu Ser Leu Arg Lys Lys Arg Pro Leu Phe Pro Trp
      80                      85                      90
Phe Gly Leu Asp Ile Gly Gly Thr Leu Val Lys Leu Val Tyr Phe
      95                      100                     105
Glu Pro Lys Asp Ile Thr Ala Glu Glu Glu Glu Glu Val Glu
      110                     115                     120
Ser Leu Lys Ser Ile Arg Lys Tyr Leu Thr Ser Asn Val Ala Tyr
      125                     130                     135
Gly Ser Thr Gly Ile Arg Asp Val His Leu Glu Leu Lys Asp Leu
      140                     145                     150
Thr Leu Cys Gly Arg Lys Gly Asn Leu His Phe Ile Arg Phe Pro
      155                     160                     165
Thr His Asp Met Pro Ala Phe Ile Gln Met Gly Arg Asp Lys Asn
      170                     175                     180
Phe Ser Ser Leu His Thr Val Phe Cys Ala Thr Gly Gly Gly Ala

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| | | | | | |
|-------------------------------------|-----|-------------------------|-----|--|-----|
| | 185 | | 190 | | 195 |
| Tyr Lys Phe Glu Gln Asp Phe Leu Thr | | Ile Gly Asp Leu Gln Leu | | | |
| | 200 | | 205 | | 210 |
| Cys Lys Leu Asp Glu Leu Asp Cys Leu | | Ile Lys Gly Ile Leu Tyr | | | |
| | 215 | | 220 | | 225 |
| Ile Asp Ser Val Gly Phe Asn Gly Arg | | Ser Gln Cys Tyr Tyr Phe | | | |
| | 230 | | 235 | | 240 |
| Glu Asn Pro Ala Asp Ser Glu Lys Cys | | Gln Lys Leu Pro Phe Asp | | | |
| | 245 | | 250 | | 255 |
| Leu Lys Asn Pro Tyr Pro Leu Leu Leu | | Val Asn Ile Gly Ser Gly | | | |
| | 260 | | 265 | | 270 |
| Val Ser Ile Leu Ala Val Tyr Ser Lys | | Asp Asn Tyr Lys Arg Val | | | |
| | 275 | | 280 | | 285 |
| Thr Gly Thr Ser Leu Gly Gly Gly Thr | | Phe Phe Gly Leu Cys Cys | | | |
| | 290 | | 295 | | 300 |
| Leu Leu Thr Gly Cys Thr Thr Phe Glu | | Glu Ala Leu Glu Met Ala | | | |
| | 305 | | 310 | | 315 |
| Ser Arg Gly Asp Ser Thr Lys Val Asp | | Lys Leu Val Arg Asp Ile | | | |
| | 320 | | 325 | | 330 |
| Tyr Gly Gly Asp Tyr Glu Arg Phe Gly | | Leu Pro Gly Trp Ala Val | | | |
| | 335 | | 340 | | 345 |
| Ala Ser Ser Phe Gly Asn Met Met Ser | | Lys Glu Lys Arg Glu Ala | | | |
| | 350 | | 355 | | 360 |
| Val Ser Lys Glu Asp Leu Ala Arg Ala | | Thr Leu Ile Thr Ile Thr | | | |
| | 365 | | 370 | | 375 |
| Asn Asn Ile Gly Ser Ile Ala Arg Met | | Cys Ala Leu Asn Glu Asn | | | |
| | 380 | | 385 | | 390 |
| Ile Asn Gln Val Val Phe Val Gly Asn | | Phe Leu Arg Ile Asn Thr | | | |
| | 395 | | 400 | | 405 |
| Ile Ala Met Arg Leu Leu Ala Tyr Ala | | Leu Asp Tyr Trp Ser Lys | | | |
| | 410 | | 415 | | 420 |
| Gly Gln Leu Lys Ala Leu Phe Ser Glu | | His Glu Gly Tyr Phe Gly | | | |
| | 425 | | 430 | | 435 |
| Ala Val Gly Ala Leu Leu Glu Leu Leu | | Lys Ile Pro | | | |
| | 440 | | 445 | | |

<210> 16

<211> 348

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7477062CD1

<400> 16

| | |
|-------------------------------------|-------------------------|
| Met Pro Gly Lys Gln Ser Glu Glu Gly | Pro Ala Glu Ala Gly Ala |
| 1 | 5 10 15 |
| Ser Glu Asp Ser Glu Glu Glu Gly | Leu Gly Leu Thr Leu Glu |
| | 20 25 30 |
| Glu Leu Gln Gln Gly Gln Glu Ala Ala | Arg Ala Leu Glu Asp Met |
| | 35 40 45 |
| Met Thr Leu Ser Ala Gln Thr Leu Val | Arg Ala Glu Val Asp Glu |
| | 50 55 60 |
| Leu Tyr Glu Glu Val Arg Pro Leu Gly | Gln Gly Arg Tyr Gly Arg |
| | 65 70 75 |

Val Leu Leu Val Thr His Arg Gln Lys Gly Thr Pro Leu Ala Leu
 80 85 90
 Lys Gln Leu Pro Lys Pro Arg Thr Ser Leu Arg Gly Phe Leu Tyr
 95 100 105
 Glu Phe Cys Val Gly Leu Ser Leu Gly Ala His Ser Ala Ile Val
 110 115 120
 Thr Ala Tyr Gly Ile Gly Ile Glu Ser Ala His Ser Tyr Ser Phe
 125 130 135
 Leu Thr Glu Pro Val Leu His Gly Asp Leu Met Ala Phe Ile Gln
 140 145 150
 Pro Lys Val Gly Leu Pro Gln Pro Ala Val His Arg Cys Ala Ala
 155 160 165
 Gln Leu Ala Ser Ala Leu Glu Tyr Ile His Ala Arg Gly Leu Val
 170 175 180
 Tyr Arg Asp Leu Lys Pro Glu Asn Val Leu Val Cys Asp Pro Ala
 185 190 195
 Cys Arg Arg Phe Lys Leu Thr Asp Phe Gly His Thr Arg Pro Arg
 200 205 210
 Gly Thr Leu Leu Arg Leu Ala Gly Pro Pro Ile Pro Tyr Thr Ala
 215 220 225
 Pro Glu Leu Cys Ala Pro Pro Pro Leu Pro Glu Gly Leu Pro Ile
 230 235 240
 Gln Pro Ala Leu Asp Ala Trp Ala Leu Gly Val Leu Leu Phe Cys
 245 250 255
 Leu Leu Thr Gly Tyr Phe Pro Trp Asp Arg Pro Leu Ala Glu Ala
 260 265 270
 Asp Pro Phe Tyr Glu Asp Phe Leu Ile Trp Gln Ala Ser Gly Gln
 275 280 285
 Pro Arg Asp Arg Pro Gln Pro Trp Phe Gly Leu Ala Ala Ala Ala
 290 295 300
 Asp Ala Leu Leu Arg Gly Leu Leu Asp Pro His Pro Arg Arg Arg
 305 310 315
 Ser Ala Val Ile Ala Ile Arg Glu His Leu Gly Arg Pro Trp Arg
 320 325 330
 Gln Arg Glu Gly Glu Ala Glu Ala Val Gly Ala Val Glu Glu Glu
 335 340 345
 Ala Gly Gln

<210> 17

<211> 341

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7477207CD1

<400> 17

Met Val Ser Ser Gln Pro Lys Tyr Asp Leu Ile Arg Glu Val Gly
 1 5 10 15
 Arg Gly Ser Tyr Gly Val Val Tyr Glu Ala Val Ile Arg Lys Thr
 20 25 30
 Ser Ala Arg Val Ala Val Lys Lys Ile Arg Cys His Ala Pro Glu
 35 40 45
 Asn Val Glu Leu Ala Leu Arg Glu Phe Trp Ala Leu Ser Ser Ile

| | | | | | |
|-----------------|-------------------------|-------------------------|-----|--|-----|
| | 50 | | 55 | | 60 |
| Lys Ser Gln His | Pro Asn Val Ile His | Leu Glu Glu Cys Ile Leu | | | |
| | 65 | | 70 | | 75 |
| Gln Lys Asp Gly | Met Val Gln Lys Met | Ser His Gly Ser Asn Ser | | | |
| | 80 | | 85 | | 90 |
| Ser Leu Tyr Leu | Gln Leu Val Glu Thr | Ser Leu Lys Gly Glu Ile | | | |
| | 95 | | 100 | | 105 |
| Ala Phe Asp Pro | Arg Ser Ala Tyr Tyr | Leu Trp Phe Val Met Asp | | | |
| | 110 | | 115 | | 120 |
| Phe Cys Asp Gly | Gly Asp Met Asn Glu Tyr | Leu Leu Ser Arg Lys | | | |
| | 125 | | 130 | | 135 |
| Pro Asn Arg Lys | Thr Asn Thr Ser Phe | Met Leu Gln Leu Ser Ser | | | |
| | 140 | | 145 | | 150 |
| Ala Leu Ala Phe | Leu His Lys Asn Gln Ile | Ile His Arg Asp Leu | | | |
| | 155 | | 160 | | 165 |
| Lys Pro Asp Asn | Ile Leu Ile Ser Gln Thr | Arg Leu Asp Thr Ser | | | |
| | 170 | | 175 | | 180 |
| Asp Leu Glu Pro | Thr Leu Lys Val Ala | Asp Phe Gly Leu Ser Lys | | | |
| | 185 | | 190 | | 195 |
| Val Cys Ser Ala | Ser Gly Gln Asn Pro | Glu Glu Pro Val Ser Val | | | |
| | 200 | | 205 | | 210 |
| Asn Lys Cys Phe | Leu Ser Thr Ala Cys | Gly Thr Asp Phe Tyr Met | | | |
| | 215 | | 220 | | 225 |
| Ala Pro Glu Val | Trp Glu Gly His Tyr | Thr Ala Lys Ala Asp Ile | | | |
| | 230 | | 235 | | 240 |
| Phe Ala Leu Gly | Ile Ile Ile Trp Ala | Met Leu Glu Arg Ile Thr | | | |
| | 245 | | 250 | | 255 |
| Phe Ile Asp Thr | Glu Thr Lys Lys Glu | Leu Leu Gly Ser Tyr Val | | | |
| | 260 | | 265 | | 270 |
| Lys Gln Gly Thr | Glu Ile Val Pro Val | Gly Glu Ala Leu Leu Glu | | | |
| | 275 | | 280 | | 285 |
| Asn Pro Lys Met | Glu Leu Leu Ile Pro | Val Lys Lys Lys Ser Met | | | |
| | 290 | | 295 | | 300 |
| Asn Gly Arg Met | Lys Gln Leu Ile Lys | Glu Met Leu Ala Ala Asn | | | |
| | 305 | | 310 | | 315 |
| Pro Gln Asp Arg | Pro Asp Ala Phe Glu | Leu Glu Leu Arg Leu Val | | | |
| | 320 | | 325 | | 330 |
| Gln Ile Ala Phe | Lys Asp Ser Ser Trp | Glu Thr | | | |
| | 335 | | 340 | | |

<210> 18

<211> 664

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 4022651CD1

<400> 18

| | | | | | |
|-----------------|---|----|----|--|--|
| Met Ala Ser Ala | Glu Thr Pro Gly Gln Trp Tyr Val Gly Pro Tyr | | | | |
| 1 | 5 | 10 | 15 | | |
| Arg Leu Glu Lys | Thr Leu Gly Lys Gly Gln Thr Gly Leu Val Lys | | | | |
| | 20 | 25 | 30 | | |
| Leu Gly Val His | Cys Val Thr Cys Gln Lys Val Ala Ile Lys Ile | | | | |
| | 35 | 40 | 45 | | |

| | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Asn | Arg | Glu | Lys | Leu | Ser | Glu | Ser | Val | Leu | Met | Lys | Val | Glu |
| | | | | 50 | | | | | 55 | | | | | 60 |
| Arg | Glu | Ile | Ala | Ile | Leu | Lys | Leu | Ile | Glu | His | Pro | His | Val | Leu |
| | | | | 65 | | | | | 70 | | | | | 75 |
| Lys | Leu | His | Asp | Val | Tyr | Glu | Asn | Lys | Lys | Tyr | Leu | Tyr | Leu | Val |
| | | | | 80 | | | | | 85 | | | | | 90 |
| Leu | Glu | His | Val | Ser | Gly | Gly | Glu | Leu | Phe | Asp | Tyr | Leu | Val | Lys |
| | | | | 95 | | | | | 100 | | | | | 105 |
| Lys | Gly | Arg | Leu | Thr | Pro | Lys | Glu | Ala | Arg | Lys | Phe | Phe | Arg | Gln |
| | | | | 110 | | | | | 115 | | | | | 120 |
| Ile | Ile | Ser | Ala | Leu | Asp | Phe | Cys | His | Ser | His | Ser | Ile | Cys | His |
| | | | | 125 | | | | | 130 | | | | | 135 |
| Arg | Asp | Leu | Lys | Pro | Glu | Asn | Leu | Leu | Leu | Asp | Glu | Lys | Asn | Asn |
| | | | | 140 | | | | | 145 | | | | | 150 |
| Ile | Arg | Ile | Ala | Asp | Phe | Gly | Met | Ala | Ser | Leu | Gln | Val | Gly | Asp |
| | | | | 155 | | | | | 160 | | | | | 165 |
| Ser | Leu | Leu | Glu | Thr | Ser | Cys | Gly | Ser | Pro | His | Tyr | Ala | Cys | Pro |
| | | | | 170 | | | | | 175 | | | | | 180 |
| Glu | Val | Ile | Arg | Gly | Glu | Lys | Tyr | Asp | Gly | Arg | Lys | Ala | Asp | Val |
| | | | | 185 | | | | | 190 | | | | | 195 |
| Trp | Ser | Cys | Gly | Val | Ile | Leu | Phe | Ala | Leu | Leu | Val | Gly | Ala | Leu |
| | | | | 200 | | | | | 205 | | | | | 210 |
| Pro | Phe | Asp | Asp | Asp | Asn | Leu | Arg | Gln | Leu | Leu | Glu | Lys | Val | Lys |
| | | | | 215 | | | | | 220 | | | | | 225 |
| Arg | Gly | Val | Phe | His | Met | Pro | His | Phe | Ile | Pro | Pro | Asp | Cys | Gln |
| | | | | 230 | | | | | 235 | | | | | 240 |
| Ser | Leu | Leu | Arg | Gly | Met | Ile | Glu | Val | Asp | Ala | Ala | Arg | Arg | Leu |
| | | | | 245 | | | | | 250 | | | | | 255 |
| Thr | Leu | Glu | His | Ile | Gln | Lys | His | Ile | Trp | Tyr | Ile | Gly | Gly | Lys |
| | | | | 260 | | | | | 265 | | | | | 270 |
| Asn | Glu | Pro | Glu | Pro | Glu | Gln | Pro | Ile | Pro | Arg | Lys | Val | Gln | Ile |
| | | | | 275 | | | | | 280 | | | | | 285 |
| Arg | Ser | Leu | Pro | Ser | Leu | Glu | Asp | Ile | Asp | Pro | Asp | Val | Leu | Asp |
| | | | | 290 | | | | | 295 | | | | | 300 |
| Ser | Met | His | Ser | Leu | Gly | Cys | Phe | Arg | Asp | Arg | Asn | Lys | Leu | Leu |
| | | | | 305 | | | | | 310 | | | | | 315 |
| Gln | Asp | Leu | Leu | Ser | Glu | Glu | Glu | Asn | Gln | Glu | Lys | Met | Ile | Tyr |
| | | | | 320 | | | | | 325 | | | | | 330 |
| Phe | Leu | Leu | Leu | Asp | Arg | Lys | Glu | Arg | Tyr | Pro | Ser | Gln | Glu | Asp |
| | | | | 335 | | | | | 340 | | | | | 345 |
| Glu | Asp | Leu | Pro | Pro | Arg | Asn | Glu | Ile | Asp | Pro | Pro | Arg | Lys | Arg |
| | | | | 350 | | | | | 355 | | | | | 360 |
| Val | Asp | Ser | Pro | Met | Leu | Asn | Arg | His | Gly | Lys | Arg | Arg | Pro | Glu |
| | | | | 365 | | | | | 370 | | | | | 375 |
| Arg | Lys | Ser | Met | Glu | Val | Leu | Ser | Val | Thr | Asp | Gly | Gly | Ser | Pro |
| | | | | 380 | | | | | 385 | | | | | 390 |
| Val | Pro | Ala | Arg | Arg | Ala | Ile | Glu | Met | Ala | Gln | His | Gly | Gln | Arg |
| | | | | 395 | | | | | 400 | | | | | 405 |
| Ser | Arg | Ser | Ile | Ser | Gly | Ala | Ser | Ser | Gly | Leu | Ser | Thr | Ser | Pro |
| | | | | 410 | | | | | 415 | | | | | 420 |
| Leu | Ser | Ser | Pro | Arg | Val | Thr | Pro | His | Pro | Ser | Pro | Arg | Gly | Ser |
| | | | | 425 | | | | | 430 | | | | | 435 |
| Pro | Leu | Pro | Thr | Pro | Lys | Gly | Thr | Pro | Val | His | Thr | Pro | Lys | Glu |
| | | | | 440 | | | | | 445 | | | | | 450 |
| Ser | Pro | Ala | Gly | Thr | Pro | Asn | Pro | Thr | Pro | Pro | Ser | Ser | Pro | Ser |
| | | | | 455 | | | | | 460 | | | | | 465 |

| | | | |
|-----------------|-------------------------|-------------------------|-----|
| Val Gly Gly Val | Pro Trp Arg Ala Arg | Leu Asn Ser Ile Lys Asn | |
| | 470 | 475 | 480 |
| Ser Phe Leu Gly | Ser Pro Arg Phe His | Arg Arg Lys Leu Gln Val | |
| | 485 | 490 | 495 |
| Pro Thr Pro Glu | Glu Met Ser Asn Leu Thr | Pro Glu Ser Ser Pro | |
| | 500 | 505 | 510 |
| Glu Leu Ala Lys | Lys Ser Trp Phe Gly | Asn Phe Ile Ser Leu Glu | |
| | 515 | 520 | 525 |
| Lys Glu Glu Gln | Ile Phe Val Val Ile | Lys Asp Lys Pro Leu Ser | |
| | 530 | 535 | 540 |
| Ser Ile Lys Ala | Asp Ile Val His Ala | Phe Leu Ser Ile Pro Ser | |
| | 545 | 550 | 555 |
| Leu Ser His Ser | Val Ile Ser Gln Thr | Ser Phe Arg Ala Glu Tyr | |
| | 560 | 565 | 570 |
| Lys Ala Thr Gly | Gly Pro Ala Val Phe | Gln Lys Pro Val Lys Phe | |
| | 575 | 580 | 585 |
| Gln Val Asp Ile | Thr Tyr Thr Glu Gly | Gly Glu Ala Gln Lys Glu | |
| | 590 | 595 | 600 |
| Asn Gly Ile Tyr | Ser Val Thr Phe Thr | Leu Leu Ser Gly Pro Ser | |
| | 605 | 610 | 615 |
| Arg Arg Phe Lys | Arg Val Val Glu Thr | Ile Gln Ala Gln Leu Leu | |
| | 620 | 625 | 630 |
| Ser Thr His Asp | Pro Pro Ala Ala Gln | His Leu Ser Asp Thr Thr | |
| | 635 | 640 | 645 |
| Asn Cys Met Glu | Met Met Thr Gly Arg | Leu Ser Lys Cys Gly Ile | |
| | 650 | 655 | 660 |
| Ile Pro Lys Ser | | | |

<210> 19

<211> 177

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7274927CD1

<400> 19

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|-----------------|---------------------|-------------------------|-----|
| Met Val Leu Leu | Ser Thr Leu Gly Ile | Val Phe Gln Gly Glu Gly | |
| 1 | 5 | 10 | 15 |
| Pro Pro Ile Ser | Ser Cys Asp Thr Gly | Thr Met Ala Asn Cys Glu | |
| | 20 | 25 | 30 |
| Arg Thr Phe Ile | Ala Ile Lys Pro Asp | Gly Val Gln Arg Gly Leu | |
| | 35 | 40 | 45 |
| Val Gly Glu Ile | Ile Lys Arg Phe Glu | Gln Lys Gly Phe Arg Leu | |
| | 50 | 55 | 60 |
| Val Gly Leu Lys | Phe Met Gln Ala Ser | Glu Asp Leu Leu Lys Glu | |
| | 65 | 70 | 75 |
| His Tyr Val Asp | Leu Lys Asp Arg Pro | Phe Phe Ala Gly Leu Val | |
| | 80 | 85 | 90 |
| Lys Tyr Met His | Ser Gly Pro Val Val | Ala Met Val Trp Glu Gly | |
| | 95 | 100 | 105 |
| Leu Asn Val Val | Lys Thr Gly Arg Val | Met Leu Gly Glu Thr Asn | |
| | 110 | 115 | 120 |
| Pro Ala Asp Ser | Lys Pro Gly Thr Ile | Arg Gly Asp Phe Cys Ile | |

| | | | | | |
|---|-----|--|-----|--|-----|
| | 125 | | 130 | | 135 |
| Gln Val Gly Arg Asn Ile Ile His Gly Ser Asp Ser Val Glu Ser | | | | | |
| | 140 | | 145 | | 150 |
| Ala Glu Lys Glu Ile Gly Leu Trp Phe His Pro Glu Glu Leu Val | | | | | |
| | 155 | | 160 | | 165 |
| Asp Tyr Thr Ser Cys Ala Gln Asn Trp Ile Tyr Glu | | | | | |
| | 170 | | 175 | | |

<210> 20

<211> 396

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7946584CD1

<400> 20

| | | |
|---|-----|---------|
| Met Gly Ala Asn Thr Ser Arg Lys Pro Pro Val Phe Asp Glu Asn | | |
| 1 | 5 | 10 15 |
| Glu Asp Val Asn Phe Asp His Phe Glu Ile Leu Arg Ala Ile Gly | | |
| | 20 | 25 30 |
| Lys Gly Ser Phe Gly Lys Val Cys Ile Val Gln Lys Asn Asp Thr | | |
| | 35 | 40 45 |
| Lys Lys Met Tyr Ala Met Lys Tyr Met Asn Lys Gln Lys Cys Val | | |
| | 50 | 55 60 |
| Glu Arg Asn Glu Val Arg Asn Val Phe Lys Glu Leu Gln Ile Met | | |
| | 65 | 70 75 |
| Gln Gly Leu Glu His Pro Phe Leu Val Asn Leu Trp Tyr Ser Phe | | |
| | 80 | 85 90 |
| Gln Asp Glu Glu Asp Met Phe Met Val Val Asp Leu Leu Leu Gly | | |
| | 95 | 100 105 |
| Gly Asp Leu Arg Tyr His Leu Gln Gln Asn Val His Phe Lys Glu | | |
| | 110 | 115 120 |
| Glu Thr Val Lys Leu Phe Ile Cys Glu Leu Val Met Ala Leu Asp | | |
| | 125 | 130 135 |
| Tyr Leu Gln Asn Gln Arg Ile Ile His Arg Asp Met Lys Pro Asp | | |
| | 140 | 145 150 |
| Asn Ile Leu Leu Asp Glu His Gly His Val His Ile Thr Asp Phe | | |
| | 155 | 160 165 |
| Asn Ile Ala Ala Met Leu Pro Arg Glu Thr Gln Ile Thr Thr Met | | |
| | 170 | 175 180 |
| Ala Gly Thr Lys Pro Tyr Met Ala Pro Glu Met Phe Ser Ser Arg | | |
| | 185 | 190 195 |
| Lys Gly Ala Gly Tyr Ser Phe Ala Val Asp Trp Trp Ser Leu Gly | | |
| | 200 | 205 210 |
| Val Thr Ala Tyr Glu Leu Leu Arg Gly Arg Arg Pro Tyr His Ile | | |
| | 215 | 220 225 |
| Arg Ser Ser Thr Ser Ser Lys Glu Ile Val His Thr Phe Glu Thr | | |
| | 230 | 235 240 |
| Thr Val Val Thr Tyr Pro Ser Ala Trp Ser Gln Glu Met Val Ser | | |
| | 245 | 250 255 |
| Leu Leu Lys Lys Leu Leu Glu Pro Asn Pro Asp Gln Arg Phe Ser | | |
| | 260 | 265 270 |
| Gln Leu Ser Asp Val Gln Asn Phe Pro Tyr Met Asn Asp Ile Asn | | |
| | 275 | 280 285 |

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Trp Asp Ala Val Phe Gln Lys Arg Leu Ile Pro Gly Phe Ile Pro
      290      295      300
Asn Lys Gly Arg Leu Asn Cys Asp Pro Thr Phe Glu Leu Glu Glu
      305      310      315
Met Ile Leu Glu Ser Lys Pro Leu His Lys Lys Lys Lys Arg Leu
      320      325      330
Ala Lys Lys Glu Lys Asp Met Arg Lys Cys Asp Ser Ser Gln Thr
      335      340      345
Cys Leu Leu Gln Glu His Leu Asp Ser Val Gln Lys Glu Phe Ile
      350      355      360
Ile Phe Asn Arg Glu Lys Val Asn Arg Asp Phe Asn Lys Arg Gln
      365      370      375
Pro Asn Leu Ala Leu Glu Gln Thr Lys Asp Pro Gln Gly Glu Asp
      380      385      390
Gly Gln Asn Asn Asn Leu
      395

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<210> 21

<211> 614

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 8088078CD1

<400> 21

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Met Glu Trp Leu Ser Pro Asp Ile Ala Leu Pro Arg Arg Asp Glu
  1      5      10      15
Trp Thr Gln Thr Ser Pro Ala Arg Lys Arg Ile Thr His Ala Lys
      20      25      30
Val Gln Gly Ala Gly Lys Ser Ile Gly Gln Leu Arg Leu Ser Ile
      35      40      45
Asp Ala Gln Asp Arg Val Leu Leu Leu His Ile Ile Glu Gly Lys
      50      55      60
Gly Leu Ile Ser Lys Gln Pro Gly Thr Cys Asp Pro Tyr Val Lys
      65      70      75
Ile Ser Leu Ile Pro Glu Asp Ser Arg Leu Arg His Gln Lys Thr
      80      85      90
Gln Thr Val Pro Asp Cys Arg Asp Pro Ala Phe His Glu His Phe
      95      100     105
Phe Phe Pro Val Gln Glu Glu Asp Asp Gln Lys Arg Leu Leu Val
      110     115     120
Thr Val Trp Asn Arg Ala Ser Gln Ser Arg Gln Ser Gly Leu Ile
      125     130     135
Gly Cys Met Ser Phe Gly Val Lys Ser Leu Leu Thr Pro Asp Lys
      140     145     150
Glu Ile Ser Gly Trp Tyr Tyr Leu Leu Gly Glu His Leu Gly Arg
      155     160     165
Thr Lys His Leu Lys Val Ala Arg Arg Arg Leu Arg Pro Leu Arg
      170     175     180
Asp Pro Leu Leu Arg Met Pro Gly Gly Gly Asp Thr Glu Asn Gly
      185     190     195
Lys Lys Leu Gln Ile Thr Ile Pro Arg Gly Lys Asp Gly Phe Gly
      200     205     210
Phe Thr Ile Cys Cys Asp Ser Pro Val Arg Val Gln Ala Val Asp

```

| | | | | | |
|-----------------|---------------------|-------------------------|-----|--|-----|
| | 215 | | 220 | | 225 |
| Ser Gly Gly Pro | Ala Glu Arg Ala Gly | Leu Gln Gln Leu Asp Thr | | | |
| | 230 | | 235 | | 240 |
| Val Leu Gln Leu | Asn Glu Arg Pro Val | Glu His Trp Lys Cys Val | | | |
| | 245 | | 250 | | 255 |
| Glu Leu Ala His | Glu Ile Arg Ser Cys | Pro Ser Glu Ile Ile Leu | | | |
| | 260 | | 265 | | 270 |
| Leu Val Trp Arg | Met Val Pro Gln Val | Lys Pro Gly Pro Asp Gly | | | |
| | 275 | | 280 | | 285 |
| Gly Val Leu Arg | Arg Ala Ser Cys Lys | Ser Thr His Asp Leu Gln | | | |
| | 290 | | 295 | | 300 |
| Ser Pro Pro Asn | Lys Arg Glu Lys Asn | Cys Thr His Gly Val Gln | | | |
| | 305 | | 310 | | 315 |
| Ala Arg Pro Glu | Gln Arg His Ser Cys | His Leu Val Cys Asp Ser | | | |
| | 320 | | 325 | | 330 |
| Ser Asp Gly Leu | Leu Leu Gly Gly Trp | Glu Arg Tyr Thr Glu Val | | | |
| | 335 | | 340 | | 345 |
| Ala Lys Arg Gly | Gly Gln His Thr Leu | Pro Ala Leu Ser Arg Ala | | | |
| | 350 | | 355 | | 360 |
| Thr Ala Pro Thr | Asp Pro Asn Tyr Ile | Ile Leu Ala Pro Leu Asn | | | |
| | 365 | | 370 | | 375 |
| Pro Gly Ser Gln | Leu Leu Arg Pro Val | Tyr Gln Glu Asp Thr Ile | | | |
| | 380 | | 385 | | 390 |
| Pro Glu Glu Ser | Gly Ser Pro Ser Lys | Gly Lys Ser Tyr Thr Gly | | | |
| | 395 | | 400 | | 405 |
| Leu Gly Lys Lys | Ser Arg Leu Met Lys | Thr Val Gln Thr Met Lys | | | |
| | 410 | | 415 | | 420 |
| Gly His Gly Asn | Tyr Gln Asn Cys Pro | Val Val Arg Pro His Ala | | | |
| | 425 | | 430 | | 435 |
| Thr His Ser Ser | Tyr Gly Thr Tyr Val | Thr Leu Ala Pro Lys Val | | | |
| | 440 | | 445 | | 450 |
| Leu Val Phe Pro | Val Phe Val Gln Pro | Leu Asp Leu Cys Asn Pro | | | |
| | 455 | | 460 | | 465 |
| Ala Arg Thr Leu | Leu Leu Ser Glu Glu | Leu Leu Leu Tyr Glu Gly | | | |
| | 470 | | 475 | | 480 |
| Arg Asn Lys Ala | Ala Glu Val Thr Leu | Phe Ala Tyr Ser Asp Leu | | | |
| | 485 | | 490 | | 495 |
| Leu Leu Phe Thr | Lys Glu Asp Glu Pro | Gly Arg Cys Asp Val Leu | | | |
| | 500 | | 505 | | 510 |
| Arg Asn Pro Leu | Tyr Leu Gln Ser Val | Lys Leu Gln Glu Gly Ser | | | |
| | 515 | | 520 | | 525 |
| Ser Glu Asp Leu | Lys Phe Cys Val Leu | Tyr Leu Ala Glu Lys Ala | | | |
| | 530 | | 535 | | 540 |
| Glu Cys Leu Phe | Thr Leu Glu Ala His | Ser Gln Glu Gln Lys Lys | | | |
| | 545 | | 550 | | 555 |
| Arg Val Cys Trp | Cys Leu Ser Glu Asn | Ile Ala Lys Gln Gln Gln | | | |
| | 560 | | 565 | | 570 |
| Leu Ala Ala Ser | Pro Pro Asp Ser Lys | Lys Leu His Pro Phe Gly | | | |
| | 575 | | 580 | | 585 |
| Ser Leu Gln Gln | Glu Met Gly Pro Val | Asn Ser Thr Asn Ala Thr | | | |
| | 590 | | 595 | | 600 |
| Gln Asp Arg Ser | Phe Thr Ser Pro Gly | Gln Thr Leu Ile Gly | | | |
| | 605 | | 610 | | |

<210> 22

<211> 484

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 2674269CD1

<400> 22

| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| Met | Ser | Thr | Glu | Gly | Arg | Leu | Pro | Ser | Cys | Ser | Ala | Cys | Val | Lys | 1 | 5 | 10 | 15 |
| Gly | Glu | Leu | Arg | Val | Leu | Thr | Ser | Ala | Ala | Leu | Thr | Ser | Arg | Asp | 20 | 25 | 30 | |
| Gly | Pro | Arg | Pro | Cys | His | Val | Leu | Phe | Arg | Ile | Val | His | Leu | Cys | 35 | 40 | 45 | |
| Leu | Arg | Lys | Ala | Asp | Gln | Lys | Leu | Val | Ile | Ile | Lys | Gln | Ile | Pro | 50 | 55 | 60 | |
| Val | Glu | Gln | Met | Thr | Lys | Glu | Glu | Arg | Gln | Ala | Ala | Gln | Asn | Glu | 65 | 70 | 75 | |
| Cys | Gln | Val | Leu | Lys | Leu | Leu | Asn | His | Pro | Asn | Val | Ile | Glu | Tyr | 80 | 85 | 90 | |
| Tyr | Glu | Asn | Phe | Leu | Glu | Asp | Lys | Ala | Leu | Met | Ile | Ala | Met | Glu | 95 | 100 | 105 | |
| Tyr | Ala | Pro | Gly | Gly | Thr | Leu | Ala | Glu | Phe | Ile | Gln | Lys | Arg | Cys | 110 | 115 | 120 | |
| Asn | Ser | Leu | Leu | Glu | Glu | Glu | Thr | Ile | Leu | His | Phe | Phe | Val | Gln | 125 | 130 | 135 | |
| Ile | Leu | Leu | Ala | Leu | His | His | Val | His | Thr | His | Leu | Ile | Leu | His | 140 | 145 | 150 | |
| Arg | Asp | Leu | Lys | Thr | Gln | Asn | Ile | Leu | Leu | Asp | Lys | His | Arg | Met | 155 | 160 | 165 | |
| Val | Val | Lys | Ile | Gly | Asp | Phe | Gly | Ile | Ser | Lys | Ile | Leu | Ser | Ser | 170 | 175 | 180 | |
| Lys | Ser | Lys | Ala | Tyr | Thr | Val | Val | Gly | Thr | Pro | Cys | Tyr | Ile | Ser | 185 | 190 | 195 | |
| Pro | Glu | Leu | Cys | Glu | Gly | Lys | Pro | Tyr | Asn | Gln | Lys | Ser | Asp | Ile | 200 | 205 | 210 | |
| Trp | Ala | Leu | Gly | Cys | Val | Leu | Tyr | Glu | Leu | Ala | Ser | Leu | Lys | Arg | 215 | 220 | 225 | |
| Ala | Phe | Glu | Ala | Ala | Asn | Leu | Pro | Ala | Leu | Val | Leu | Lys | Ile | Met | 230 | 235 | 240 | |
| Ser | Gly | Thr | Phe | Ala | Pro | Ile | Ser | Asp | Arg | Tyr | Ser | Pro | Glu | Leu | 245 | 250 | 255 | |
| Arg | Gln | Leu | Val | Leu | Ser | Leu | Leu | Ser | Leu | Glu | Pro | Ala | Gln | Arg | 260 | 265 | 270 | |
| Pro | Pro | Leu | Ser | His | Ile | Met | Ala | Gln | Pro | Leu | Cys | Ile | Arg | Ala | 275 | 280 | 285 | |
| Leu | Leu | Asn | Leu | His | Thr | Asp | Val | Gly | Ser | Val | Arg | Met | Arg | Arg | 290 | 295 | 300 | |
| Pro | Val | Gln | Gly | Gln | Arg | Ala | Val | Leu | Gly | Gly | Arg | Val | Trp | Ala | 305 | 310 | 315 | |
| Pro | Ser | Gly | Ser | Thr | Gly | Gly | Leu | Arg | Gln | Arg | Glu | Thr | Trp | Gly | 320 | 325 | 330 | |
| Lys | Ser | Ser | Leu | Pro | Ala | Cys | Arg | Asn | Val | Arg | Arg | Val | Phe | Val | 335 | 340 | 345 | |
| Leu | Arg | Pro | Pro | Ser | Val | Leu | Gln | Gly | Arg | Glu | Val | Arg | Gly | Pro | 350 | 355 | 360 | |

Gln Gln His Arg Glu Gln Asp His Gln Cys Pro Leu Gln Arg Tyr
 365 370 375
 Pro Pro Gly Thr Cys Glu Ala Ser His Pro Thr Thr Thr Val Val
 380 385 390
 Ser Val Cys Leu Gly Trp Trp Ala Gly His Pro Pro Ala Ala Ala
 395 400 405
 Asn Ala Gln His Arg Gly Gly Pro Gly Gly Ser Trp Ala His Ala
 410 415 420
 Glu Ser Arg Arg His Ala Leu Trp Ala Ser His Pro Val Gly Gly
 425 430 435
 Pro Thr Pro Arg Cys Arg Arg Arg Gln Ser Pro Ser Trp Gly Ser
 440 445 450
 Gly Ala Ala Thr Ala Pro Val His Leu Ala Phe Pro Gly Gly Pro
 455 460 465
 Val Gly Cys Asp His Gln Ala Arg Gly Leu Trp Gly Leu Leu His
 470 475 480
 Cys Leu Pro Asp

<210> 23

<211> 460

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7472409CD1

<400> 23

Met Glu Lys Tyr Glu Arg Ile Arg Val Val Gly Arg Gly Ala Phe
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 Gly Ile Val His Leu Cys Leu Arg Lys Ala Asp Gln Lys Leu Val
 20 25 30
 Ile Ile Lys Gln Ile Pro Val Glu Gln Met Thr Lys Glu Glu Arg
 35 40 45
 Gln Ala Ala Gln Asn Glu Cys Gln Val Leu Lys Leu Leu Asn His
 50 55 60
 Pro Asn Val Ile Glu Tyr Tyr Glu Asn Phe Leu Glu Asp Lys Ala
 65 70 75
 Leu Met Ile Ala Met Glu Tyr Ala Pro Gly Gly Thr Leu Ala Glu
 80 85 90
 Phe Ile Gln Lys Arg Cys Asn Ser Leu Leu Glu Glu Glu Thr Ile
 95 100 105
 Leu His Phe Phe Val Gln Ile Leu Leu Ala Leu His His Val His
 110 115 120
 Thr His Leu Ile Leu His Arg Asp Leu Lys Thr Gln Asn Ile Leu
 125 130 135
 Leu Asp Lys His Arg Met Val Val Lys Ile Gly Asp Phe Gly Ile
 140 145 150
 Ser Lys Ile Leu Ser Ser Lys Ser Lys Ala Tyr Thr Val Val Gly
 155 160 165
 Thr Pro Cys Tyr Ile Ser Pro Glu Leu Cys Glu Gly Lys Pro Tyr
 170 175 180
 Asn Gln Lys Ser Asp Ile Trp Ala Leu Gly Cys Val Leu Tyr Glu
 185 190 195
 Leu Ala Ser Leu Lys Arg Ala Phe Glu Ala Ala Asn Leu Pro Ala

| | | | | | |
|---|-----|--|-----|--|-----|
| | 200 | | 205 | | 210 |
| Leu Val Leu Lys Ile Met Ser Gly Thr Phe Ala Pro Ile Ser Asp | | | | | |
| | 215 | | 220 | | 225 |
| Arg Tyr Ser Pro Glu Leu Arg Gln Leu Val Leu Ser Leu Leu Ser | | | | | |
| | 230 | | 235 | | 240 |
| Leu Glu Pro Ala Gln Arg Pro Pro Leu Ser His Ile Met Ala Gln | | | | | |
| | 245 | | 250 | | 255 |
| Pro Leu Cys Ile Arg Ala Leu Leu Asn Leu His Thr Asp Val Gly | | | | | |
| | 260 | | 265 | | 270 |
| Ser Val Arg Met Arg Arg Pro Val Gln Gly Gln Arg Ala Val Leu | | | | | |
| | 275 | | 280 | | 285 |
| Gly Gly Arg Val Trp Ala Pro Ser Gly Ser Thr Gly Gly Leu Arg | | | | | |
| | 290 | | 295 | | 300 |
| Gln Arg Glu Thr Trp Gly Lys Ser Ser Leu Pro Ala Cys Arg Asn | | | | | |
| | 305 | | 310 | | 315 |
| Val Arg Arg Val Phe Val Leu Arg Pro Pro Ser Val Leu Gln Gly | | | | | |
| | 320 | | 325 | | 330 |
| Arg Glu Val Arg Gly Pro Gln Gln His Arg Glu Gln Asp His Gln | | | | | |
| | 335 | | 340 | | 345 |
| Cys Pro Leu Gln Arg Tyr Pro Pro Gly Thr Cys Glu Ala Ser His | | | | | |
| | 350 | | 355 | | 360 |
| Pro Thr Thr Thr Val Val Ser Val Cys Leu Gly Trp Trp Ala Gly | | | | | |
| | 365 | | 370 | | 375 |
| His Pro Pro Ala Ala Ala Asn Ala Gln His Arg Gly Gly Pro Gly | | | | | |
| | 380 | | 385 | | 390 |
| Gly Ser Trp Ala His Ala Glu Ser Arg Arg His Ala Leu Trp Ala | | | | | |
| | 395 | | 400 | | 405 |
| Ser His Pro Val Gly Gly Pro Thr Pro Arg Cys Arg Arg Arg Gln | | | | | |
| | 410 | | 415 | | 420 |
| Ser Pro Ser Trp Gly Ser Gly Ala Ala Thr Ala Pro Val His Leu | | | | | |
| | 425 | | 430 | | 435 |
| Ala Phe Pro Gly Gly Pro Val Gly Cys Asp His Gln Ala Arg Gly | | | | | |
| | 440 | | 445 | | 450 |
| Leu Trp Gly Leu Leu His Cys Leu Pro Asp | | | | | |
| | 455 | | 460 | | |

<210> 24

<211> 1413

<212> PRT

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7477484CD1

<400> 24

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|---|----|----|----|
| Met Pro Ala Pro Gly Ala Leu Ile Leu Leu Ala Ala Val Ser Ala | | | |
| 1 | 5 | 10 | 15 |
| Ser Gly Cys Leu Ala Ser Pro Ala His Pro Asp Gly Phe Ala Leu | | | |
| | 20 | 25 | 30 |
| Gly Arg Ala Pro Leu Ala Pro Pro Tyr Ala Val Val Leu Ile Ser | | | |
| | 35 | 40 | 45 |
| Cys Ser Gly Leu Leu Ala Phe Ile Phe Leu Leu Leu Thr Cys Leu | | | |
| | 50 | 55 | 60 |
| Cys Cys Lys Arg Gly Asp Val Gly Phe Lys Glu Phe Glu Asn Pro | | | |
| | 65 | 70 | 75 |

| | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Gly | Glu | Asp | Cys | Ser | Gly | Glu | Tyr | Thr | Pro | Pro | Ala | Glu | Glu | 80 | 85 | 90 |
| Thr | Ser | Ser | Ser | Gln | Ser | Leu | Pro | Asp | Val | Tyr | Ile | Leu | Pro | Leu | 95 | 100 | 105 |
| Ala | Glu | Val | Ser | Leu | Pro | Met | Pro | Ala | Pro | Gln | Pro | Ser | His | Ser | 110 | 115 | 120 |
| Asp | Met | Thr | Thr | Pro | Leu | Gly | Leu | Ser | Arg | Gln | His | Leu | Ser | Tyr | 125 | 130 | 135 |
| Leu | Gln | Glu | Ile | Gly | Ser | Gly | Trp | Phe | Gly | Lys | Val | Ile | Leu | Gly | 140 | 145 | 150 |
| Glu | Ile | Phe | Ser | Asp | Tyr | Thr | Pro | Ala | Gln | Val | Val | Val | Lys | Glu | 155 | 160 | 165 |
| Leu | Arg | Ala | Ser | Ala | Gly | Pro | Leu | Glu | Gln | Arg | Lys | Phe | Ile | Ser | 170 | 175 | 180 |
| Glu | Ala | Gln | Pro | Tyr | Arg | Ser | Leu | Gln | His | Pro | Asn | Val | Leu | Gln | 185 | 190 | 195 |
| Cys | Leu | Gly | Leu | Cys | Val | Glu | Thr | Leu | Pro | Phe | Leu | Leu | Ile | Met | 200 | 205 | 210 |
| Glu | Phe | Cys | Gln | Leu | Gly | Asp | Leu | Lys | Arg | Tyr | Leu | Arg | Ala | Gln | 215 | 220 | 225 |
| Arg | Pro | Pro | Glu | Gly | Leu | Ser | Pro | Glu | Leu | Pro | Pro | Arg | Asp | Leu | 230 | 235 | 240 |
| Arg | Thr | Leu | Gln | Arg | Met | Gly | Leu | Glu | Ile | Ala | Arg | Gly | Leu | Ala | 245 | 250 | 255 |
| His | Leu | His | Ser | His | Asn | Tyr | Val | His | Ser | Asp | Leu | Ala | Leu | Arg | 260 | 265 | 270 |
| Asn | Cys | Leu | Leu | Thr | Ser | Asp | Leu | Thr | Val | Arg | Ile | Gly | Asp | Tyr | 275 | 280 | 285 |
| Gly | Leu | Ala | His | Ser | Asn | Tyr | Lys | Glu | Asp | Tyr | Tyr | Leu | Thr | Pro | 290 | 295 | 300 |
| Glu | Arg | Leu | Trp | Ile | Pro | Leu | Arg | Trp | Ala | Ala | Pro | Glu | Leu | Leu | 305 | 310 | 315 |
| Gly | Glu | Leu | His | Gly | Thr | Phe | Met | Val | Val | Asp | Gln | Ser | Arg | Glu | 320 | 325 | 330 |
| Ser | Asn | Ile | Trp | Ser | Leu | Gly | Val | Thr | Leu | Trp | Glu | Leu | Phe | Glu | 335 | 340 | 345 |
| Phe | Gly | Ala | Gln | Pro | Tyr | Arg | His | Leu | Ser | Asp | Glu | Glu | Val | Leu | 350 | 355 | 360 |
| Ala | Phe | Val | Val | Arg | Gln | Gln | His | Val | Lys | Leu | Ala | Arg | Pro | Arg | 365 | 370 | 375 |
| Leu | Lys | Leu | Pro | Tyr | Ala | Asp | Tyr | Trp | Tyr | Asp | Ile | Leu | Gln | Ser | 380 | 385 | 390 |
| Cys | Trp | Arg | Pro | Pro | Ala | Gln | Arg | Pro | Ser | Ala | Ser | Asp | Leu | Gln | 395 | 400 | 405 |
| Leu | Gln | Leu | Thr | Tyr | Leu | Leu | Ser | Glu | Arg | Pro | Pro | Arg | Pro | Pro | 410 | 415 | 420 |
| Pro | Pro | Pro | Pro | Pro | Pro | Arg | Asp | Gly | Pro | Phe | Pro | Trp | Pro | Trp | 425 | 430 | 435 |
| Pro | Pro | Ala | His | Ser | Ala | Pro | Arg | Pro | Gly | Thr | Leu | Ser | Ser | Pro | 440 | 445 | 450 |
| Phe | Pro | Leu | Leu | Asp | Gly | Phe | Pro | Gly | Ala | Asp | Pro | Asp | Asp | Val | 455 | 460 | 465 |
| Leu | Thr | Val | Thr | Glu | Ser | Ser | Arg | Gly | Leu | Asn | Leu | Glu | Cys | Leu | 470 | 475 | 480 |
| Trp | Glu | Lys | Ala | Arg | Arg | Gly | Ala | Gly | Arg | Gly | Gly | Gly | Ala | Pro | 485 | 490 | 495 |

| | | |
|-----------------|---------------------|-------------------------|
| Ala Trp Gln Pro | Ala Ser Ala Pro Pro | Ala Pro His Ala Asn Pro |
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| Ser Asn Pro Phe | Tyr Glu Ala Leu Ser | Thr Pro Ser Val Leu Pro |
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| Val Ile Ser Ala | Arg Ser Pro Ser Val | Ser Ser Glu Tyr Tyr Ile |
| 530 | 535 | 540 |
| Arg Leu Glu Glu | His Gly Ser Pro Pro | Glu Pro Leu Phe Pro Asn |
| 545 | 550 | 555 |
| Asp Trp Asp Pro | Leu Asp Pro Gly Val | Pro Ala Pro Gln Ala Pro |
| 560 | 565 | 570 |
| Gln Ala Pro Ser | Glu Val Pro Gln Leu | Val Ser Glu Thr Trp Ala |
| 575 | 580 | 585 |
| Ser Pro Leu Phe | Pro Ala Pro Arg Pro | Phe Pro Ala Gln Ser Ser |
| 590 | 595 | 600 |
| Ala Ser Gly Ser | Phe Leu Leu Ser Gly | Trp Asp Pro Glu Gly Arg |
| 605 | 610 | 615 |
| Gly Ala Gly Glu | Thr Leu Ala Gly Asp | Pro Ala Glu Val Leu Gly |
| 620 | 625 | 630 |
| Glu Arg Gly Thr | Ala Pro Trp Val Glu | Glu Glu Glu Glu Glu Glu |
| 635 | 640 | 645 |
| Glu Gly Ser Ser | Pro Gly Glu Asp Ser | Ser Ser Leu Gly Gly Arg |
| 650 | 655 | 660 |
| Leu Leu Ala Ala | Gly Arg Ala Gly Leu | Pro Gly Arg Leu Ala His |
| 665 | 670 | 675 |
| Gly Pro Pro Ala | Ser Ala Pro Pro Glu | Phe Leu Asp Pro Leu Met |
| 680 | 685 | 690 |
| Gly Ala Ala Ala | Pro Gln Tyr Pro Gly | Arg Gly Pro Pro Pro Ala |
| 695 | 700 | 705 |
| Pro Pro Pro Pro | Pro Pro Pro Pro Arg | Ala Pro Ala Asp Pro Ala |
| 710 | 715 | 720 |
| Ala Ser Pro Asp | Pro Pro Ser Ala Val | Ala Ser Pro Gly Ser Gly |
| 725 | 730 | 735 |
| Leu Ser Ser Pro | Gly Pro Lys Pro Gly | Asp Ser Gly Tyr Glu Thr |
| 740 | 745 | 750 |
| Glu Thr Pro Phe | Ser Pro Glu Gly Ala | Phe Pro Gly Gly Gly Ala |
| 755 | 760 | 765 |
| Ala Glu Glu Glu | Gly Val Pro Arg Pro | Arg Ala Pro Pro Glu Pro |
| 770 | 775 | 780 |
| Pro Asp Pro Gly | Ala Pro Arg Pro Pro | Pro Asp Pro Gly Pro Leu |
| 785 | 790 | 795 |
| Pro Leu Pro Gly | Pro Arg Glu Lys Pro | Thr Phe Val Val Gln Val |
| 800 | 805 | 810 |
| Ser Thr Glu Gln | Leu Leu Met Ser Leu | Arg Glu Asp Val Thr Arg |
| 815 | 820 | 825 |
| Asn Leu Leu Gly | Glu Lys Gly Ala Thr | Ala Arg Glu Thr Gly Pro |
| 830 | 835 | 840 |
| Arg Lys Ala Gly | Arg Gly Pro Gly Asn | Arg Glu Lys Val Pro Gly |
| 845 | 850 | 855 |
| Leu Asn Arg Asp | Pro Thr Val Leu Gly | Asn Gly Lys Gln Ala Pro |
| 860 | 865 | 870 |
| Ser Leu Ser Leu | Pro Val Asn Gly Val | Thr Val Leu Glu Asn Gly |
| 875 | 880 | 885 |
| Asp Gln Arg Ala | Pro Gly Ile Glu Glu | Lys Ala Ala Glu Asn Gly |
| 890 | 895 | 900 |
| Ala Leu Gly Ser | Pro Glu Arg Glu Glu | Lys Val Leu Glu Asn Gly |
| 905 | 910 | 915 |

| | | |
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| Glu Leu Arg Ser Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly | | |
| 935 | 940 | 945 |
| Gly Leu Thr Pro Pro Lys Ser Glu Asp Lys Val Ser Glu Asn Gly | | |
| 950 | 955 | 960 |
| Gly Leu Arg Phe Pro Arg Asn Thr Glu Arg Pro Pro Glu Thr Gly | | |
| 965 | 970 | 975 |
| Pro Trp Arg Ala Pro Gly Pro Trp Glu Lys Thr Pro Glu Ser Trp | | |
| 980 | 985 | 990 |
| Gly Pro Ala Pro Thr Ile Gly Glu Pro Ala Pro Glu Thr Ser Leu | | |
| 995 | 1000 | 1005 |
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| Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu Gly Ser Gly | | |
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| Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly Gly Pro | | |
| 1070 | 1075 | 1080 |
| Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr Arg | | |
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| Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln | | |
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| Ala Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly | | |
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| Lys Gly Pro Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro | | |
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| Gln Gly Asn Ser Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser | | |
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| Leu Ala Leu Pro Pro Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly | | |
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| 1280 | 1285 | 1290 |
| Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys Met Val Ser | | |
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| Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu Thr Pro | | |
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| Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr Asp | | |
| 1325 | 1330 | 1335 |

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<223> Incyte ID No: 55056054CB1

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<211> 3161

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 7481989CB1

<400> 35

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<211> 3538

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 55052990CB1

<400> 36

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<211> 3047

<212> DNA

<213> Homo sapiens

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<223> Incyte ID No: 7482377CB1

<400> 37

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<210> 39

<211> 1719

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 5850001CB1

<400> 39

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<210> 40

<211> 1156

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7477062CB1

<400> 40

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<210> 41
 <211> 1096
 <212> DNA
 <213> Homo sapiens

<220>
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 <223> Incyte ID No: 7477207CB1

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<210> 42
 <211> 2647
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <223> Incyte ID No: 4022651CB1

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<400> 42
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<210> 43

<211> 864

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 7274927CB1

<400> 43

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gcagacacac aaacagaaaa ttggactaca gtgctaagat gctgtaagaa gaggttaact 180
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ccttcattgc gatcaaacca gatgggggtcc agcgggggtct tgtgggagag attatcaagc 360
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<210> 44

<211> 1594

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No.: 7946584CB1

<400> 44

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acaaggtgag gatggtcaga ataacaactt gtaa 1594

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<210> 45

<211> 1845

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<223> Incyte ID No: 8088078CB1

<400> 45

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<210> 46

<211> 1680

<212> DNA

<213> Homo sapiens

<220>

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<223> Incyte ID No: 2674269CB1

<400> 46

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